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Poster

PSTR001: Glial Development

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Title: Expression of the glutamate transporter GLAST in metamorphosed larvae of the Pacific Sea biscuit Dendraster excentricus.

Authors: *A. COLORES MENDOZA;
Intituto de investigaciones oceanologicas, Univ. de autónoma de Baja California, ENSENADA, Mexico

Abstract: Expression of the glutamate transporter GLAST in metamorphosed larvae of the Pacific Sea biscuit *Dendraster excentricus*.

Authors*A.V. COLORES-MENDOZA[1], P.I. DE LEÓN-VILLALOBOS[1], J.G. CORREA-REYES[1], L.M. ENRIQUEZ-PAREDES[2], A. ORTEGA[3], T.N. OLIVARES-BAÑUELOS[1].
[1]Instituto de Investigaciones Oceanológicas, Universidad Autónoma de Baja California, Ensenada México, C.P. 22780. [2]Facultad de Ciencias Marinas, Universidad Autónoma de Baja California, Ensenada México, C.P. 22780. [3]Departamento de Toxicología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, Ciudad de México, 07000, México.

Abstract: Marine invertebrates are strategic models for neuroscience. In these organisms, glial cells share structural and functional characteristics with chordates, which facilitates the study of these important neuronal cells. Among the characteristics of glial cells are glutamate transporter systems, whose function is to maintain adequate levels of glutamate in the synaptic cleft to prevent degeneration and even death of neuronal cells. The biological importance of glial cells in the CNS, together with the presence of a large number of phylogenetically conserved structures, makes these cells important targets for biomedical research. Considering the above, the general objective of the present work was to identify, through cellular and molecular techniques, the expression of the glutamate transporter GLAST in metamorphosed larvae of the sea biscuit *Dendraster excentricus*. The genetic expression of this exclusive transporter of glial cells was corroborated by qPCR, and the identification and localization of the GLAST protein by Western blot and immunofluorescence assays in metamorphosed sea biscuit larvae from the coasts of Baja California. After these tests we observed the specific expression of GLAST in the nerve terminals of the metamorphosed larvae. The study of glial cells in echinoderms represents an advance in the understanding of the mechanisms involved in the formation of these neuronal cells in invertebrates, and their possible implications for treatments against neurodegenerative diseases.

Disclosures
A.V. Colores-Mendoza: None. P.I. De León-Villalobos: None. J.G. Correa-Reyes: None. L.M. Enriquez-Paredes: None. A. Ortega: None. T.N. Olivares-Bañuelos: None.**Poster**

PSTR001: Glial Development

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 5R35NS105094-07

Title: Unveiling Conserved Mechanisms of Astrocytic Glia Development Using Caenorhabditis elegans CEPsh Glia

Authors: *S. LIU, S. SHAHAM;
The Rockefeller Univ., New York, NY

Abstract: Vertebrate astrocytic glial cells are crucial for brain development and function, exhibiting remarkable diversity in morphology, molecular signatures, and physiological functions. Despite their importance, the precise mechanisms governing astrocyte specification and the generation of distinct astrocyte subtypes are not fully understood. The four *Caenorhabditis elegans* CEPsh glia are a homologous glial cell type of mammalian astrocytes. CEPsh glia envelop the central neuropil of *C. elegans* (the nerve ring), and resemble astrocytes in their elaborate morphology, development from radial-glia-like precursors, postembryonic transcriptomes, and physiological functions. Each of the four CEPsh glial cells arises from a different position in the invariant *C. elegans* cell lineage, and is, therefore, likely generated by a distinct developmental program. Thus, *C. elegans* CEPsh glia provide an excellent setting to understand astrocyte fate determination and the emergence of astrocyte diversity. Using single-cell RNA sequencing, we obtained a transcriptome of all four newly generated CEPsh glia, as well as their direct progenitor cells and their close relatives. We identified several conserved genes governing CEPsh glia development. These include the distal-less homeobox transcription factor gene *ceh-43*, whose mammalian ortholog, *Dlx1/2*, regulates the decision of neural stem cells to generate either GABAergic interneurons or astrocytes and oligodendrocytes; and β-catenin and TCF genes whose homologs function in the mammalian cortex to maintain radial glia stem cell identity and self-renewal. Other conserved genes were identified as well. Together, our studies should allow us to now define a core program driving astrocyte formation across animals.

Disclosures: S. Liu: None. **S. Shaham:** None.

Poster

PSTR001: Glial Development

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: NAIST Overseas Dispatch Support FY2024 R6290003 (to H.W)
Japanese Government (Monbukagakusho: MEXT) Scholarship 2020 #200287 (to H.W)
JSPS KAKENHI Grant Number JP21K06189 (to R.A)

Title: The role of fibroblast growth factors in peripheral nerve development in zebrafish lateral line organ

Authors: *H. WONG, T. MATSUI, Y. BESSHO, R. AKIYAMA;
Div. of Biol. Sci., Nara Inst. of Sci. and Technol., Ikoma, Japan

Abstract: Development of the sensory organ relies on the coordinated regulation of primordium, peripheral nerves, and surrounding glial cells. However, the molecular mechanisms concomitantly orchestrating the development of these cell types are not fully understood. To investigate this, we utilized the zebrafish lateral line, a sensory organ that detects water flow. During lateral line organ development, primordium migrates and guides the extension of lateral line axons. Schwann cell precursors migrate and divide along the axons, and eventually differentiating into myelinating Schwann cells for axonal ensheathment. Here, we revisited the double knockout (dKO) zebrafish for Fgf3 and Fgf10a, known regulators of lateral line primordium morphogenesis and migration, and newly identified in axon bundling defects in the lateral line nerve of dKO embryo. dKO showed excessive proliferation of Schwann cells, one of the regulators of axon bundling structure, indicating that Fgf3,10a are the upstream regulators of Schwann cells in lateral line nerves. Moreover, proliferated Schwann cells in dKO abnormally invaded the interspace between axons, indicating a link between excessive Schwann cell proliferation and axon bundle malformation. Chemical inhibition of Schwann cell proliferation in dKO rescued the axon bundling defect, suggesting the role of excessively proliferated Schwann cells in causing this defect. Overall, these results suggest that Fgf3 and Fgf10a regulate the proliferation of Schwann cells and peripheral nerve morphology in addition to lateral line primordium development.

Disclosures: H. Wong: None. **T. Matsui:** None. **Y. Bessho:** None. **R. Akiyama:** None.

Poster

PSTR001: Glial Development

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Title: Laminin α3 expression influences the expression of GFAP in the developing spinal cord

Authors: *T. YAMAURA[1], R. SAKUMA[2], S. MAEDA[4], T. TACHIBANA[3], H. YAGI[5]; [1]Hyogo Med. Univ., Hyogo, Japan; [3]Orthopaedic Surgery, [2]Hyogo Med. Univ., Nishinomiya, Japan; [4]Dept. of Anat. and Cell Biol., Hyogo Col. of Mediciene, Nishinomiya-Shi, Japan; [5]Dept. of Anat. and Cell Biol., Hyogo Col. of Med., Nishinomiya, Japan

Abstract: The extracellular matrix (ECM) plays several important roles in the development, maintenance, and regeneration of the nervous system. Laminins, one of the major groups of ECM proteins, are hetero trimetric molecules composed of one alpha, one beta, and one gamma chain. While there are several reports about the expression of laminins in the developing central nervous system, it is not fully unveiled detail expression of laminins during the development of the spinal cord. We investigated the expression patterns and physiological functions of laminins in the development of the spinal cord.C57BL/6J mouse embryos were used for immunohistochemical and molecular biological analyses. To visualize neural projections, 1,1′-dioctadecyl-6,6′-di(4-sulfophenyl)-3,3,3′,3′-tetramethylindocarbocyanine (DiI) crystals were injected into the embryonic spinal cord. OS3 cells, a mouse glial progenitor cell line, and primary cultured spinal glial cells were used to evaluate the effects of laminins.In the immunohistochemical analysis, laminin α3 was expressed in the marginal zone (prospective white matter) in E12 and E14. The immunoreactivity against laminin α3 covered the neuronal axons in the marginal zone of the spinal cord, as development progressed, the intensity of laminin α3 in the marginal zone decreased. Neurons that projected neurites in the white matter of the E14 spinal cord were labeled in the spinal cord and brainstem by DiI injection. Neurons located in the DiI-labeled area expressed laminin α3 mRNA. These results suggest that spinal cord and brainstem neurons that expressed laminin α3 mRNA projected their axons to the marginal zone and laminin α3 covered their axons in the marginal zone. To investigate the function of laminin α3 in the developing white matter of the spinal cord, we evaluated the development of glial cells using immunohistochemical analysis. GFAP, which is expressed in astrocytes, was upregulated in the white matter of the spinal cord where laminin α3 expression was observed. We observed that the expression of GFAP was upregulated when OS3 cells and primary cultured spinal glial cells were cultured on the laminin composed of α3 chain.These results suggested that the laminin α3 that was produced by neurons and expressed in the white matter of the developing spinal cord was involved in astrocyte differentiation in the developing mouse spinal cord.

Disclosures: **T. Yamaura:** None. **R. Sakuma:** None. **S. Maeda:** None. **T. Tachibana:** None. **H. Yagi:** None.

Poster

PSTR001: Glial Development

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01NS121660
NCI P30CA118100
Taconic-Cyagen Custom Animal Model Awards

Title: The critical role of Contactin-1 in myelination of white matter tracts during brain development

Authors: *H. CHEN[1], L. PAEZ-BELTRAN[2], T. VUE[3];
[1]Univ. of New Mexico, Albuquerque, NM; [2]Univ. of New Mexico Dept. of Neurosciences, Albuquerque, NM; [3]Dept. of Neurosciences, Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM

Abstract: Contactin-1 (CNTN1), a cell adhesion and cell surface molecule, has been shown to be important for cell migration, axon guidance, myelination, and synaptogenesis. Indeed, CNTN1 is suggested to be required for neuronal and glial intercommunication to maintain a strong synaptic contact and regulation of axonal ion channels. This study aims to elucidate the role CNTN1 plays in the development of the central nervous system (CNS) by analyzing changes in brain morphology and myelination of major brain regions using Cntn1 knock-out (KO) and conditional knock-out (cKO) mice. With both global KO and oligodendrocyte precursor cell (OPC) specific cKO, a decreased in OLIG2+ cells and myelination in major white matter tracts (corpus callosum, internal capsule) was observed, resulting in a decreased in thickness of these tracts. This finding demonstrates that CNTN1 plays an important role in establishing a healthy myelin network in maintaining brain integrity and proper insulation and protection to the axons.

Disclosures: H. Chen: None. **L. Paez-Beltran:** None. **T. Vue:** None.

Poster

PSTR001: Glial Development

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Program #/Poster #: PSTR001.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: Netherlands Organization for Scientific Research - ZonMW
Pitt-hopkins UK
Pitt-hopkins NL

Title: Myelination and remyelination deficits in a Pitt-Hopkins syndrome animal model

Authors: *L. BAIONA ALVES[1], M. SMIDT[2], S. MESMAN[3];
[1]Univ. of Amsterdam - Swammerdam Inst. for Life Sci., Maarssen, Netherlands; [2]MNS, Uva, Amsterdam, Netherlands; [3]Univ. of Amsterdam, Amsterdam, Netherlands

Abstract: Pitt-Hopkins syndrome (PTHS) is a syndromic form of Autism Spectrum Disorder (ASD) caused by haploinsufficiency of TCF4. Although PTHS is a neurodevelopmental disorder recent developments suggest oligodendrogenesis is implicated in PTHS due to multiple patients showing delayed myelination. In addition, *in vitro* culture systems show that TCF4 mutations play a role in the differentiation of oligodendrocyte precursor cells, although it is unknown how TCF4 regulates this process. We decided to test the response of our Pitt-Hopkins animal model to a demyelinating compound (cuprizone) and subsequent brain remyelination, in order to test whether Tcf4 haplotypes show fragilized oligodendrogenesis and to what extent remyelination is impaired. This question is of great importance to patients, especially as remyelinating drugs might be considered for therapeutics. In order to solve this issue, we subjected a Tcf4 mouse model, to a cuprizone induced demyelination program (5 weeks exposure of 0.2% cuprizone in food, remyelination period of 3 weeks), to observe the demyelination and remyelination rate between $Tcf4^{+/+}$ and $Tcf4^{+/-}$ animals versus their respective no-cuprizone exposed controls (4 groups, n=3 for each group). In addition to Luxol Blue staining which detects white matter tracts, we also utilized immunohistochemistry for Myelin Basic Protein (Mbp) which stains myelin fibers and Neurofilament 200 which stains the cytoskeleton of neurons, in order to better characterize structural features within the Corpus Callossum area. We find that the Medial Corpus Callossum Thickness (MCCT) is smaller in $Tcf4^{+/-}$ animals when comparing to $Tcf4^{+/+}$ animals prior to treatment with cuprizone. After demyelination by cuprizone, the MCCT of $Tcf4^{+/+}$ animals is reduced, resembling the initial MCCT of $Tcf4^{+/-}$ animals. The $Tcf4^{+/-}$ animals exposed to cuprizone show smaller MCCT when comparing to their respective control, although the decrease is not as severe. When looking at Luxol Blue Intensity in the Lateral Corpus Callossum (LCC) a profound demyelinating effect is observed, with this effect being more prominent in $Tcf4^{+/-}$ animals, showing us that these animals have an increased response to demyelination when comparing to wild types. When testing for remyelination, there is no detectable remyelination in $Tcf4^{+/-}$ animals in contrast to $Tcf4^{+/+}$ animals. These results, indicate that Pitt-Hopkins animal models show myelination problems in adulthood, displaying aggravated responses to cuprizone demyelination and slower remyelination, opening a window for treatment paradigms.

Disclosures: **L. Baiona Alves:** None. **M. Smidt:** None. **S. Mesman:** None.

Poster

PSTR001: Glial Development

Location: MCP Hall A

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Program #/Poster #: PSTR001.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH NINDS R01NS096100

Title: Developmental elimination sculpts the cortical astrocyte population

Authors: *K. M. MARKEY[1], K. CASE[2], A. GARCIA[3];
[1]Drexel Univ., Philadelphia, PA; [2]Neurosci., Drexel Univ. Col. of Med., Philadelphia, PA; [3]Dept. of Biol., Drexel Univ., Philadelphia, PA

Abstract: Developmental elimination sculpts the cortical astrocyte populationEstablishment of proper cell number is vital for the proper construction of the centralnervous system (CNS). Here we focus on astrocytes, a major class of glial cell in the CNS,which have important roles in synapse formation and function. How the brain achievesthe correct number of astrocytes is poorly understood. Developmental elimination ofneurons and oligodendrocytes is well established and is accomplished by both apoptosisas well as non -apoptotic microglial engulfment of cells during their respectivedevelopmental period. Whether astrocytes experience developmental elimination tosculpt the adult population, and the timing and mechanism by which this is achieved, isnot well understood. In this study, we focus on cortical astrocytes during postnataldevelopment, the period during which these cells are generated and undergo maturation.We investigated whether cortical astrocytes are eliminated during the early postnatalperiod. Immunostaining with the microglia marker Iba1 and astrocyte marker Sox9revealed that astrocytes are engulfed by microglia cups. We examined tissues betweenP1 and P10 and found that microglial engulfment is most pronounced at postnatal day(P)7. Further evaluation with the apoptosis marker, cleaved caspase 3, indicates thatastrocytes at P7 are not undergoing apoptosis, suggesting that engulfed astrocytes areotherwise viable cells. Colocalization analysis with Iba1, Sox9 and the proliferation marker,Ki67, demonstrated that engulfed astrocytes are postmitotic. We next investigatedwhether astrocytes undergo elimination during late postnatal development. Stereologicalanalysis shows that cortical astrocyte number declines between P14 to P28 and stabilizesinto adulthood. Colocalization analysis with Sox9 and cleaved caspase 3 suggests thatat P28 astrocytes are undergoing apoptosis but not at P14, P21 or P24. Taken togethermy data suggest that the cortex employs two mechanisms at two developmental stagesto establish the mature cortical astrocyte population. Ongoing work will determine whetherastrocyte elimination occurs in a lineage dependent manner and the molecularmechanism that underlies astrocyte survival.

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Poster

PSTR001: Glial Development

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF Graduate Research Fellowship Program #1745302
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Hock E. Tan and K. Lisa Yang Center for Autism Research at MIT
Yang Tan Collective at MIT
Poitras Center for Psychiatric Disorders Research at MIT
Stanley Center for Psychiatric Research at Broad Institute
NIH BRAIN Initiative UM1MH130981
K. Lisa Yang and Hock E. Tan Center for Molecular Therapeutics in Neuroscience

Title: A transcriptomic atlas of astrocyte regional heterogeneity across developmental stages in mouse and marmoset brains

Authors: M. SCHROEDER[1], ***D. MCCORMACK**[1], L. METZNER[1], K. LI[1], Q. ZHANG[1], H. ZANIEWSKI[1], K. LEVANDOWSKI[2], E. S. BOYDEN[1,3], F. M. KRIENEN[4], G. FENG[1]; [1]McGovern Inst. for Brain Res., MIT Brain and Cognitive Sci., Cambridge, MA; [2]Stanley Ctr. for Psychiatric Res., Broad Inst. of MIT and Harvard, Cambridge, MA; [3]Howard Hughes Medical Institute, Chevy Chase, MD; [4]Neurosci., Princeton Univ., Princeton, NJ

Abstract: Recent single-cell and earlier bulk RNA sequencing studies have demonstrated significant transcriptomic heterogeneity among astrocytes, particularly across brain regions. However, the developmental trajectory of this heterogeneity and its conservation across species requires further systematic study. To this end, we used single-nucleus RNA sequencing to characterize the molecular diversity of brain cells across developmental stages (late embryonic, neonate, early and late adolescent, young adult, and late adult) and four brain regions (prefrontal cortex (PFC), motor cortex, striatum, and thalamus) in the mouse and marmoset brain. Our analysis of over 150,000 single astrocyte nuclei revealed striking regional heterogeneity among astrocytes, particularly between telencephalic and diencephalic regions, at all developmental time points surveyed in both species. To investigate when and how regional patterning in astrocytes occurs, we calculated differentially expressed genes between developmental time points both within and across brain regions. Some regional differences are present throughout development, but many genes are transiently expressed in early development while others appear at later stages of maturity. We employ cell-cell interaction analysis to infer which elements of astrocyte regional heterogeneity may be developed in response to the needs of the local environment as opposed to patterned embryonically. We used multiplexed fluorescence in situ hybridization to validate the differential expression of selected genes in astrocytes in the PFC, striatum, and thalamus of neonate and adult mouse and marmoset brains (n = 4 mice, n = 2 marmosets per time point). We also demonstrate results of our efforts to characterize region-specific astrocyte morphology and protein localization using expansion microscopy. Using a viral delivery approach in Aldh1l1-Cre mice, we demonstrate ~18-fold expansion of GFP-labeled astrocytes, co-stained with vascular and synaptic markers to visualize astrocytic contacts with these structures. We use semi-automated tracing software to model and quantify measures of astrocyte morphology across PFC, striatum, and thalamus. Furthermore, we have achieved the first viral-mediated brain-wide fluorescent labeling of astrocytes in the marmoset and demonstrate proof of concept for their expansion. More broadly, this cross-species, cross-development, cross-region molecular and morphological profile of brain cells using consistent experimental and computational methodology is a valuable resource for the field.

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Poster

PSTR001: Glial Development

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01MH125956-03

Title: Uncovering astrocyte heterogeneity in the developing human brain

Authors: ***N. KEBEDE**[1], A. SING[1], P. CHOPRA[1], D. J. CUTLER[2,1], S. A. SLOAN[1]; [1]Human Genet., [2]Emory Univ., Atlanta, GA

Abstract: Astrocytes differ widely in their morphology, function, and contribution to disease; however, the developmental basis for this diversity remains unresolved. Distinct astrocytes may arise from homogenous progenitors that diversify in response to their local environment. Conversely, their heterogenous fates may be hardwired from development. Here, we sought to examine the diversity of astrocytes in the developing human cortex and the unique mechanisms of their specification. To resolve astrocyte diversity, we performed single-cell RNA sequencing on glial populations isolated from primary fetal cortical tissue post-gliogenic switch. Transcriptional analysis revealed two distinct astrocyte populations with unique gene expression patterns. Notably, these distinctions persist when integrated with published transcriptomic datasets. Using RNAscope, we experimentally validated these non-overlapping astrocyte populations. Furthermore, leveraging differentially expressed surface proteins, we can isolate these populations via fluorescence activated cell sorting (FACS) to perform bulk RNA sequencing. We are continuing to resolve the origins and cell fate mechanisms of these distinct astrocyte populations. Gene expression patterns suggest that the two populations show differential responses to sonic hedgehog (SHH) signaling. We are investigating the relevance of this canonical developmental signaling pathway in astrocyte development by probing the impact of SHH activation and GLI protein activity on cell fate determination. These efforts to characterize distinct lineages in development can lead to a more nuanced understanding of the diverse contributions of human cortical astrocytes to development, disease, and repair.

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Poster

PSTR001: Glial Development

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Topic: A.01. Neurogenesis and Gliogenesis

Support: U01MH122590 (NIMH) to S.D.
BX005160 (U.S. Department of Veterans Affairs) to S.D.

Title: Profiling gene expression and H3K27ac histone modification in oligodendrocyte precursor cells throughout human postnatal development.

Authors: *A. KOZLENKOV[1], F. NAQING[2], Z. DUREN[2], S. DRACHEVA[3];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Clemson Univ., Greenwood, SC; [3]Dept. Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Oligodendroglial (OLIG) lineage cells constitute the largest proportion of non-neuronal cells in human brain, with essential functions in the generation and maintenance of axonal myelination and in supporting neuronal homeostasis. Whereas the majority of OLIGs are differentiated oligodendrocytes at different stages of maturation (hereafter: MOs), OLIGs also comprise a smaller population of dividing oligodendrocyte precursor cells (OPC), which persist into adulthood and are crucial for generation of new MO cells during development, learning, or recovery from trauma or disease. OPCs have been implicated in a number of neurodevelopmental and neurodegenerative disorders (i.e., schizophrenia, depression, multiple sclerosis, Alzheimer's disease). Nevertheless, OPCs are still insufficiently studied, partly due to their relatively small numbers (~2-4% of all brain cells in adult human brain) and the lack of efficient methods to isolate them from autopsied brain specimens. Recently (Kozlenkov et. al, 2024, Glia), we introduced a novel approach to purify OPC and MO nuclei from human postmortem brain. Using this approach, we have now performed an extensive transcriptomic profiling of human OPCs and MOs across the whole span of human postnatal development and ageing. We sampled dorsolateral prefrontal cortex tissue from ~60 neurotypical donors, whose age at the time of death ranged from 5 weeks to 77 years old covering all major age groups. These groups included neonatal period (age 0), infancy (ages 1-2), early childhood (ages 3-6), late childhood (ages 8-12), adolescence (ages 14-18), early adulthood (ages 20-45), and adulthood (>45 years old). In addition to the RNA-seq, we performed ChIP-seq analysis in samples from ~30 donors to profile the H3K27ac histone mark, which is associated with active gene regulatory regions (promoters and enhancers). This allowed us to correlate these regions' activity with gene expression data. In both OPCs and MOs, we detected multiple differentially expressed genes in pairwise comparisons between all age groups, with major changes occurring during the early periods of postnatal development. In contrast, only few changes were detected between early adult and adult groups. Similar findings were observed using the H3K27ac ChIP-seq data, with the detection of large number of differentially acetylated peaks during early postnatal development. The aggregated analysis of RNA-seq and ChIP-seq data also allowed us to get insights into key transcription factors and epigenetic programs that are active during human postnatal development, as well as into potential roles of disease-associated genes and processes.

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Poster

PSTR001: Glial Development

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Topic: A.01. Neurogenesis and Gliogenesis

Support: RO1 AA02711
T32 ES007026
P30 ES001247
F31 ES35614-1

Title: Effects of gestational and lactational exposure to perfluorohexanoic acid (PFHxA) on cerebellum development

Authors: *E. PLUNK[1], L. H. LE[2], K. MANZ[3], M. SOBOLEWSKI[4], A. K. MAJEWSKA[5]; [1]Envrn. Med., Univ. of Rochester, Rochester, NY; [2]Univ. of Rochester, Rochester, NY; [3]Dept. of Envrn. Hlth. Sci., Univ. of Michigan, Ann Arbor, MI 48109, Ann Arbor, MI; [4]Univ. of Rochester Med. Ctr., Rochester, NY; [5]Neurosci., Univ. of Rochester, Rochester, NY

Abstract: Gestational exposures to legacy per- and polyfluoroalkyl substances (PFAS) have been associated with neurodevelopmental disorders, leading industries to replace them with next generation, short-chain PFAS, including perfluorohexanoic acid (PFHxA). However, the developmental neurotoxicology of these alternatives has not been characterized. Filling this gap is critically important as PFHxA is increasingly found in the serum of pregnant women and in breast milk, as well as in the brains of adults postmortem. The cerebellum shows some of the highest PFHxA concentrations, and due to its long window of maturation, may be particularly sensitive to PFAS exposure contributing to neurobehavioral deficits. Given that legacy PFAS suppress the peripheral immune system, it is critical to evaluate of the effect of PFHxA on the function of microglia, which are the immune cells of the brain and play critical functions in neurodevelopment. To test the hypothesis that PFHxA inhibits microglial function, in turn, preventing proper maturation of cerebellar circuits and altering behavior, we exposed pregnant C57Bl/6 mice daily from gestational day 0 through postnatal day (P) 21 to ddH2O, a lower (0.32 mg/kg of body weight (bw)) or higher (50 mg/kg of bw) dose of PFHxA using treat based, oral administration. Using mass spectrometry, we showed that exposure resulted in PFHxA levels that were similar in males and females and were dose-dependent in both the serum and brain at P21. Cerebellar transcriptomic profiles showed downregulation of microglia transcripts in females at both doses at this age. Preliminary immunohistochemical analyses suggest that these transcriptomic changes results from PFHxA-induced alterations in microglia density but not morphology in specific cerebellar layers, however these effects were observed in both sexes. To determine whether PFHxA exposure resulted in long-term behavioral deficits we used the open field test (OFT) and elevated plus maze (EPM) to assess activity and “anxiety-like” behaviors in

adulthood. In the OFT, we found that males display a hypoactive phenotype in both treatment groups, while female activity levels are not affected. Additionally, in the EPM we found that males displayed an “anxiety-like” phenotype in only the lower treatment group suggesting nonmonotonic effects, while female behavior was not affected. Together these data suggest that PFHxA exposure may impact cerebellar microglia perturbing the development of cerebellar circuitry which in turn influences behavior. This highlights the importance of evaluating the neurotoxicity of this PFAS in the context of neurocircuitry development in the cerebellum.

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Poster

PSTR001: Glial Development

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Program #/Poster #: PSTR001.12/A12

Topic: A.01. Neurogenesis and Gliogenesis

Support: Larry L. Hillblom Foundation
CIRM Bridges

Title: Investigating brain developement in human and nonhuman primate derived forebrain organoids

Authors: *J. PRATT[1], S. FERNANDES[2], C. MARCHETTO[3], A. SHARMA[4], F. H. GAGE[5], D. M. KLEIN[4];
[1]Salk Inst. for Biol. Studies, Chula Vista, CA; [2]LOG-G, Salk Inst., El Cajon, CA; [3]LOGG, Universoty of California San Diego, La Jolla, CA; [4]Salk Inst. for Biol. Studies, La Jolla, CA; [5]LOG-G, Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: Relative to humans, some features of brain development and maturation have been shown to occur earlier in nonhuman primates (NHPs). Understanding these variations in neoteny across species can reveal unique developmental processes, uncovering ways in which the brain functions. Using protocols developed by Dr. Guo-Li Ming’s lab, we have generated forebrain organoids (FBOs) from human and NHP induced and embryonic pluripotent stem cells (iPSC and ESCs). FBOs are a valuable in vitro model for studying processes of brain development, as they have the ability to recapitulate complex cytoarchitecture, neural network formation, and some features of neurological diseases. We have successfully generated FBOs from a diverse range of primate ESC and iPSC lines including humans, rhesus macaques, chimpanzees, bonobos, and marmosets. FBO generation was performed with the intention of investigating features of neoteny in humans compared to NHP-derived FBOs. qPCR analysis revealed notable trends in the early upregulation of GFAP+ astrocytes in NHP FBOs relative to controls. This data was corroborated through immunohistochemical analysis (IHC), unveiling a conspicuous increase in GFAP+ astrocytes in NHP FBOs at day 70, suggesting earlier gliogenesis compared

to humans. Furthermore, qPCR analysis identified the downregulation of genes associated with the migration and maturation of specific neuronal populations during brain development in NHPs at days 50 and 100, suggesting that these neuronal migration events are concluding earlier in NHPs compared to humans. Genes involved in neural progenitor cell proliferation and synapse formation, were transcriptionally upregulated at day 50 in NHP FBOs. Differences in gene expression profiles may indicate an accelerated onset of cortical thickening and gyrification in NHPs. Finally, there were increases in GABA+ neurons in NHPs relative to humans at day 70, but a uniformity across species became apparent by day 225. With GABA being an inhibitory neurotransmitter that plays a role in fine-tuning neural networks, this delay we see in humans could be a contributing factor to cortical complexity. These findings provide evidence for distinct developmental trajectories across human and nonhuman primate species.

Disclosures: J. Pratt: None. **S. Fernandes:** None. **C. Marchetto:** None. **A. Sharma:** None. **F.H. Gage:** None. **D.M. Klein:** None.

Poster

PSTR001: Glial Development

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.13/A13

Topic: A.01. Neurogenesis and Gliogenesis

Support: Fondecyt Regular Grant 1240486

Title: The ciliary proteins IIIG9 and PP1 alpha, form a protein complex in adherens junction of polarized ependymal and MDCK cells

Authors: *K. SALAZAR MARTINEZ[1], M. OVIEDO[1], E. RAMÍREZ[2], F. A. MARTINEZ ACUÑA[3], F. J. NUALART[4];
[1]Univ. de Concepción, Concepcion, Chile; [2]Univ. of Concepción, Concepcion, Chile; [3]Dept. de Biologia Celular, Facultad de Cs Biológicas., Univ. of Concepcion, Concepcion, Chile; [4]Cell Biol., Univ. de Concepción, Concepcion, Chile

Abstract: MDCK and ependymal cells are two polarized cells whose study allows the identification of new molecular mechanisms that determine or maintain epithelial polarization and could be limit the development of neoplastic events. Initially, IIIG9 has been proposed how a novel PP1 regulatory subunit (PPP1R32) in ependymal cells, where it has been localized in the cilia like a dotted pattern and in the adherens junctions. However, it is unknown if in these regions, IIIG9 is necessary for the specific function of PP1. On the other hands, PP1 catalytic subunits (α, β, γ) are highly conservative and ubiquitous Ser/Thr phosphatases, where PP1α function is important for the biology of polarized cells, for example, localizing in the cilia of *Chlamydomonas* or in the cell junctions of MDCK cells. We have characterized the expression of PP1 subunits in ependymal cells by qRT-PCR coupled with LMD technique and *in situ* hybridization. The colocalization of catalytic isoforms of PP1 and IIIG9 was analyzed by

confocal microscopy *in situ* and *in vitro*, showing that IIIG9 and PP1α colocalized in cilia and adherens junctions. Similar analyses were done in 2D and 3D (cystos) MDCK cultures. By FRET analysis we define the *in vitro* interaction between IIIG9 and PP1α in HEK cells. Finally, by proximity ligation assays in adult brain and in 2D and 3D MDCK cell culture and in adult brain, we define the IIIG9/PP1α interaction in the adherens junctions and in the cilia. Our data confirm the IIIG9/ PP1α interaction in ependymal cells and MDCK cells and this condition may be decisive in driving the subcellular action of phosphatase 1 in adherent junctions and cilia of polarized cells.

Disclosures: K. Salazar Martinez: None. **M. Oviedo:** None. **E. Ramírez:** None. **F.A. Martinez Acuña:** None. **F.J. Nualart:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.01/A14

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI (24K10490, 23H02795, 22K15638, 20H03339, 20K16490, 19H01007, 17H06312, 17K19442, 16H04670, 15H02358)
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Takeda Science Foundation
Toyoaki Scholarship Foundation
Nakatomi Foundation

Title: Ca^{2+} signalling drives nuclear deformation cycles underlying radial migration of immature cortical neurons

Authors: *S.-I. HORIGANE[1,2,3], S. TAKEMOTO-KIMURA[1,2,3], S. KAMIJO[3], H. FUJII[3], H. BITO[3];
[1]Res. Inst. of Envrn. Med., Nagoya Univ., Nagoya, Japan; [2]Mol. Cell. Neurosci., Nagoya Univ. Grad Sch. of Med., Nagoya, Japan; [3]Neurochem., The Univ. of Tokyo Grad. Sch. of Med., Tokyo, Japan

Abstract: Ca^{2+} critically regulates neural circuit formation, yet how Ca^{2+} signalling in immature neurons governs formation of a brain architecture remains obscure. During corticogenesis, migrating neurons undergo cycles of nucleus rounding/elongation linked to migratory movements. Here, we identified polarized Ca^{2+} transients at the cell rear, promoting radial migration through nuclear rounding. Forced Ca^{2+} elevation facilitated migratory movement and actomyosin-mediated cell rear retraction that pushed the nucleus forward and induced rounding.

Conversely, sustained and excessive Ca^{2+} elevation locked in the nuclear shape and hindered cell migration, suggesting that cycles of moderate Ca^{2+} transients supported physiological amounts of migration. L-type voltage-dependent Ca^{2+} channels were necessary for cell rear Ca^{2+} transients. By contrast, a gain-of-function mutation associated with autism spectrum disorder caused abnormal nucleus rounding and impaired radial migration. Our findings thus reveal essential roles of cyclic and polarized Ca^{2+} signalling in an activity-dependent speed control mechanism that orchestrates nuclear deformation and radial migration.

Disclosures: S. Horigane: None. **S. Takemoto-Kimura:** None. **S. Kamijo:** None. **H. Fujii:** None. **H. Bito:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.02/A15

Topic: A.01. Neurogenesis and Gliogenesis

Support: Coordenação de Aperfeiçoamento de Pessoal de Ensino Superior (CAPES)
Conselho Nacional de Pesquisa (CNPq)
Fundação de Amparo à Pesquisa do Rio de Janeiro (FAPERJ)

Title: Dynamics of prenatal and postnatal cellularity of the developing human brain in typical and pathological conditions

Authors: *E. CASTRO FONSECA[1,2], D. FERREIRA[3], G. DE ARAÚJO GONZAGA[3,2], I. RABELLO[3], J. FERREIRA[3], J. PIRES[3], B. ROSA[3], C. BATISTA[3], J. DOS SANTOS FREITAS[3], V. MORAIS[3], A. MAIA[3], I. PRAXEDES[4], A. GUASTAVINO[5], C. ESTEVES[5], G. CHALFUN[5], A. PRATA-BARBOSA[5,2], L. CHIMELLI[6], R. E.P LEITE[7,8], C. SUEMOTO[7,8], W. JACOB FILHO[7,8], R. NITRINI[7,9], C. A. PASQUALUCCI[7,10], L. GRINBERG[11,12,10], F. TOVAR-MOLL[13], P. GARCEZ[3,14], R. LENT[3,2,15];
[1]Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil., Rio de Janeiro, Brazil; [2]D'Or Institute for Research and Education, Rio de Janeiro, Brazil; [3]Inst. of Biomed. Sci., Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [4]Dept. of Pathology, Maternity Sch., Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [5]Dept. of Neonatology, Maternity Sch., Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [6]Lab. of Neuropathology, Rio de Janeiro State Brain Inst., Rio de Janeiro, Brazil; [7]Biobank for Aging Studies (LIM 22), Univ. of São Paulo Med. Sch., São Paulo, Brazil; [8]Laboratory of Medical Research in Aging (LIM 66), University of São Paulo Medical School, São Paulo, Brazil; [9]Department of Neurology, University of São Paulo Medical School, São Paulo, Brazil; [10]Department of Pathology, University of São Paulo Medical School, São Paulo, Brazil; [11]Memory and Aging Ctr., Dept. of Neurol., Univ. of California, San Francisco, CA; [12]Biobank for Aging Studies (LIM 22), University of São Paulo Medical School, São Paulo,

Brazil; [13]D'Or Inst. for Res. and Educ., Rio de Janeiro, Brazil; [14]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom; [15]National Institute of Translational Neuroscience, Ministry of Science and Technology, Brazil

Abstract: Despite the great advances in techniques to study the brain, some fundamental data remain unclear, such as the absolute number of brain cells in the different stages of life. There is great cell proliferation during development, but it is not well established if the final cell number found in adults is reached before or after birth. Here, we describe the first results of a novel study on the developing human brain, aiming to determine its absolute cellular composition using the isotropic fractionator technique. Our approach seeks to reveal the absolute numbers of neurons and other cells for each region, define the neuron/glia ratio, and compare this cellularity between different structures. 23 brains (12 males and 11 females) have been donated by parents or caregivers, aged from 26 gestation weeks to 7 postnatal months. All procedures were approved by institutional ethics committees. Preliminary immunohistochemical results have shown that NeuN is a specific nuclear marker for neurons at the studied gestational ages; that is, it does not co-localize with nuclear markers for other cell types. However, current data suggest that it does not label the entire population of immature neurons (HuC/D+), which are relevant for early developmental ages. Quantitative data on cellularity show a linear increase in the number of mature neurons (NeuN+) in the cerebrum in the last trimester of gestation until the first 7 months of age. On the other hand, the cerebellum showed an exponential increase of neurons (NeuN+) between the last trimester and the first 3 months of postnatal life. During this period, non-neuronal cells increase at a more accelerated speed in the cerebrum than in the cerebellum. At term birth, there is a lower number of brain neurons (NeuN+) than in adults, mainly because the number of neurons in the cerebellum is much lower, only 7% of the adult number, suggesting intensive postnatal neurogenesis in this region. In contrast, the cerebrum at birth displays already about 65% of the adult neuronal number. The number of all brain non-neuronal cells was significantly lower than that found in adults, suggesting intense postnatal gliogenesis. We also studied a case with congenital syphilis and compared it with a typical, age-paired control. We observed significantly lower numbers of neurons (NeuN+) and non-neuronal cells in the telencephalon and cerebellum. In conclusion, the absolute quantification of cells along human brain development is an important tool to reveal the dynamics of neurogenesis and gliogenesis for different regions of interest and to understand it better both at typical conditions and under pathological constraints that affect the normal brain development.

Disclosures: E. Castro Fonseca: None. **D. Ferreira:** None. **G. de Araújo Gonzaga:** None. **I. Rabello:** None. **J. Ferreira:** None. **J. Pires:** None. **B. Rosa:** None. **C. Batista:** None. **J. dos santos freitas:** None. **V. Morais:** None. **A. Maia:** None. **I. Praxedes:** None. **A. Guastavino:** None. **C. Esteves:** None. **G. Chalfun:** None. **A. Prata-Barbosa:** None. **L. Chimelli:** None. **R. E.P Leite:** None. **C. Suemoto:** None. **W. Jacob Filho:** None. **R. Nitrini:** None. **C. A. Pasqualucci:** None. **L. Grinberg:** None. **F. Tovar-Moll:** None. **P. Garcez:** None. **R. Lent:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.03/A16

Topic: A.01. Neurogenesis and Gliogenesis

Title: Alteration in morphology of neural progenitors in Down syndrome human fetal neocortex

Authors: *E. CAPRA, N. KALEBIC;
Human Technopole, Milan, Italy

Abstract: Down syndrome (DS) is the most frequent autosomal aneuploidy and the most common genomic disorder of intellectual disability. It is caused by the partial or total trisomy of human chromosome 21 (HC21). DS fetal brain development is characterised by impaired neurogenesis and reduced size of several cortical regions, which in turns causes cognitive disabilities of several degrees. However, the causes underlying these reductions are poorly known. Considering that the vast majority of human cortical neurons is generated by basal or outer radial glia (bRG or oRG), we focused on differences in bRG cell biology in trisomic brains. We have previously described that bRG proliferation, and therefore the production rate of neurons, is strongly linked with bRG morphology, especially the number of cellular protrusions these cells grow. Here, we investigated whether the link between cell proliferation and morphology could be at a base of the developmental impairment in DS fetal brain. We analysed the frontal lobe of human fetal trisomic and euploid brains from 12 to 15 post-conception weeks (pcw) through histology and microscopy techniques. To analyse the obtained images, we developed a machine-learning-assissted image analysis pipeline for the automatic segmentation of nuclei based on total nuclei staining and assignment of positivity to specific nuclear markers. We detected a significant decrease in the abundance of bRG in trisomic samples compared to age-matching euploid controls. We further observed a significant difference in the distribution of bRG morphotypes in trisomic brains. Interestingly, we observed a reduction in the relative proportion of those morphotypes presenting multiple cellular protrusions compared to normally-developing controls. These in turn could provide a potential explanation for the reduced neurogenesis in DS fetal brains. This study allow us to explore a new and thus far poorly explored direction in developmental neuroscience, stating that not only key mitotic events but also the morphology of neural progenitors might be critical for the development of the human brain, and that alterations in progenitor morphology could lead to impairment in neurodevelopment.

Disclosures: E. Capra: None. **N. Kalebic:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.04/A17

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01NS093009

Title: The role of Lmx1a in the formation of mossy fiber pathway and hippocampal development

Authors: *I. ISKUSNYKH, N. FATTAKHOV, M. KIRCHNER, A. ZAKHAROVA, S. CERVANTES ABRAHAM, E. STESHINA, V. V. CHIZHIKOV;
Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Neuronal proliferation, differentiation, and migration in the CNS are regulated by secreted molecules produced by specialized signaling centers. Besides the production of secreted molecules and growth factors, signaling centers also give rise to specific neuronal populations. The cortical hem (CH) is one such signaling center, which is located in the telencephalic dorsal midline and is responsible for hippocampal formation. In our previous studies, we identified the LIM-homeodomain transcription factor Lmx1a as an important regulator of CH development. *Lmx1a* regulates the expression of Wnt3a - a major CH-derived signaling molecule that promotes the proliferation of progenitors in the dentate neuroepithelium and subsequent dentate gyrus development. Also, via *Eomes*, *Lmx1a* controls the migration of CH-derived Cajal-Retzius neurons regulating hippocampal fissure formation, which develops adjacent to the dentate gyrus. It remains unknown, however, whether Lmx1a is involved in the development of any other hippocampal regions beyond the dentate gyrus and what downstream genes are direct transcriptional targets of Lmx1a. Interestingly, our current study revealed a significant reduction in the thickness of mossy fibers, identified by immunohistochemistry against Calbindin, in CA2 and CA3 hippocampal regions in Lmx1a deficient mice, indicating the role of Lmx1a in the formation of hippocampal mossy fiber pathway. Also, we screened mouse *Wnt3a* and *Eomes* genomic regions for Lmx1a binding sites and identified four putative Lmx1a-dependent regulatory elements (RE). These RE were located both upstream and downstream of *Eomes* and *Wnt3a* genes and were conserved across multiple mammalian species. Our ongoing analysis will identify the functional significance of these Lmx1a binding sites for *Wnt3a* and *Eomes* expression. Taken together, our data indicate that Lmx1a is a regulatory gene that is important for the formation of the hippocampal mossy fiber pathway in CA2 and CA3 regions of the hippocampus and suggest that in the telencephalon, *Eomes* and *Wnt3a* are direct transcriptional targets of Lmx1a.

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Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.05/A18

Topic: A.01. Neurogenesis and Gliogenesis

Support: NASA/INSGC
BBSRC
Valparairo University

Title: The extracellular glycoprotein Nell2 promotes neuronal survival in the developing and aging retina

Authors: C. NAKAMOTO[1], C. MEYERS[1], A. CARNEY[1], E. ROEGLIN[2], A. NICHOLS[1], O. BLACKKETTER[1], G. LANDWERLEN[1], T. BENZ[1], ***M. NAKAMOTO**[3];
[1]Biol., Valparaiso Univ., Valparaiso, IN; [2]Psychology, Valparaiso Univ., Valparaiso, IN; [3]Valparaiso Univ., Valparaiso, IN

Abstract: Correct functioning of the nervous system is critically dependent on the generation and maintenance of the proper numbers of neurons. During development, a significant portion of the newly generated neurons die through programmed cell death, and neuronal survival is maintained only if they encounter appropriate environmental cues. Once neurons are selected for survival during the developmental cell death period, the proper numbers of neurons are normally maintained for the lifetime of the organism. Whereas previous studies have revealed factors that regulate developmental neuronal survival, the molecular mechanisms that control the generation of proper numbers of neurons during development and support the long-term neuronal survival in the adult and aging brain are not fully understood. Nell2 (also known as Nel) is a multi-modular extracellular glycoprotein that is predominantly expressed in the nervous system. Nell2 exerts diverse functions in neural development, including regulation of neuronal proliferation and differentiation, and axon guidance. Our previous study has shown that Nell2 acts as an inhibitory guidance cue for retinal axons in the eye-specific retinogeniculate projection. Nell2 has been shown to promote survival of neurons prepared from cerebral cortex and hippocampus *in vitro* and protect retinal ganglion cells (RGCs) from cell death after optic nerve injury *in vivo*. We have previously demonstrated that Nell2 positively regulates the RGC numbers by promoting their differentiation and survival in the developing chick retina. In this study, we have investigated survival-promoting functions of Nell2 in the developing and aging retina by using Nell2 knockout mice. Nell2 is strongly expressed in RGCs in developing and adult mice. We have found that the numbers of RGCs are significantly decreased in developing (embryonic day (E) 19.5 – postnatal day (P) 4) Nell2 knockout mice. Deletion of the Nell2 gene does not significantly affect neuronal proliferation. However, Nell2 knockout mice showed increased apoptosis in developing RGCs. In addition, compared to wild-type mice, continuous decrease in RGC numbers and increase in apoptotic RGCs were found in the aging (~P480) Nell2 knockout mice. Furthermore, we detected expression Ros1, a receptor tyrosine kinase that binds to Nell2, in RGCs by immunohistochemistry. Taken together, those results suggest that Nells acts as a survival promoting factor that is essential for production and maintenance of proper numbers of RGCs, and that Ros-1 may act as a receptor for Nell2 in RGCs.

Disclosures: C. Nakamoto: None. **C. Meyers:** None. **A. Carney:** None. **E. Roeglin:** None. **A. Nichols:** None. **O. Blackketter:** None. **G. Landwerlen:** None. **T. Benz:** None. **M. Nakamoto:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.06/A19

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH/NIAAA R01 AA027269

Title: Cell death in the rat thalamic nucleus reuniens following one-day alcohol exposure on postnatal day 9

Authors: *C. P. BODNER, S. C. GUSTAFSON, I. F. SMITH, G. E. LYONS, A. Y. KLINTSOVA;
Psychological and Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Fetal alcohol spectrum disorders (FASD) can result from alcohol exposure (AE) in utero. Specifically, AE during the brain growth spurt (BGS)—a period of rapid neurodevelopment in the third trimester— may result in impaired executive functioning (EF) and working memory deficits, which rely on the coordination of activity between the prefrontal cortex and the hippocampus by the thalamic nucleus reuniens (Re). To model human AE during the BGS, we employed a rodent model, where the BGS occurred in the first two weeks of postnatal (PD) life in Long-Evans rats. Previous work in our lab has shown that single-day AE on PD7 leads to cell death in the Re 12 hours after exposure, resulting in significant reductions in cell number on PD72 driven by neuron loss. The current work expands on prior findings by examining the Re after a single-day AE on PD9 at either 12 hours or 56 days (PD65) after exposure to determine if 1) Re is vulnerable to the teratogenic effects of ethanol when exposed on PD9, and 2) apoptosis at PD9 translates to decreased cell population later in life. On PD9, pups were intragastrically intubated with alcohol (AEmod (3 g/kg) or AEhigh (5.25 g/kg)) mixed with milk formula or were sham intubated (SI). Pups were perfused 12 hours or 56 days after AE. Brains were extracted, sectioned coronally maintaining order, and every 8th section containing Re was stained with cresyl violet. Apoptotic cell number and total cell number in the Re were estimated using unbiased stereology. One-way ANOVA analysis showed that 12 hours after AE, there was a significant effect of postnatal treatment on the number of apoptotic cells [$F(2, 23) = 46.87$, $p < .0001$]. Post hoc tests revealed that AEhigh resulted in significantly more apoptotic cells [M = 214.1; SD = 68.39] when compared to SI [M= 37.23; SD = 12.64] and AEmod [M = 70.25; SD = 51.38]. Two-Way ANOVA analysis showed there was an interaction effect between sex and PD treatment on the number of apoptotic cells [$F(1,18) = 5.81$, $p = 0.02$], such that females experienced significantly more cell death in the Re after high AE [M=252.93; SD=22.48] than males [M=175.33; SD=81.68]. PD65 analysis showed no interactions between sex and postnatal treatment on the total cell number in the Re [$F(1, 29) = 0.37$, $p = 0.55$]. There were also no main effects of sex [$F(1, 29) = 0.15$, $p = 0.70$] or treatment on total cell number in the Re [$F(1, 29) = 3.46$, $p = 0.07$]. Together, these data suggest that high AE on PD9 causes cell death, and females are especially sensitive to these teratogenic effects. Effects on total cell

number in Re were not maintained into adulthood which raises the need to evaluate phenotypic cell populations to confirm lasting vulnerability of the thalamic Re to AE during the BGS.

Disclosures: C.P. Bodner: None. **S.C. Gustafson:** None. **I.F. Smith:** None. **G.E. Lyons:** None. **A.Y. Klintsova:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.07/A20

Topic: A.01. Neurogenesis and Gliogenesis

Title: Intravital imaging of dynamic neural cell migration and interaction in the embryonic brain

Authors: *Z. LONG;
Tsinghua Univ., Beijing, China

Abstract: Neural cell migration is essential for shaping the developing neocortex, an evolutionarily advanced brain structure that computes higher motor, sensory and cognitive functions. Throughout their migration, neurons respond to guidance cues and interact extensively with the surrounding cellular environment, which includes other neurons, progenitors, oligodendrocytes, and vascular structures. However, the migration patterns of various neuronal types and their interactions with microglia in the developing neocortex are not well understood. Additionally, conventional methods of brain slice imaging, which often cause irreversible damage to embryonic brain vasculature and immune systems, prove inadequate for studying these phenomena. Therefore, we have developed an innovative approach for long-term intravital imaging of externally immobilized embryos that allows deep tissue penetration, high temporal-spatial resolution, and supports multiple color channels for multi-directional observation. This technique preserves blood supply up to five hours, and ensure normal brain development. Utilizing this method alongside transgenic mouse labeling, we have characterized three distinct migration strategies employed by newborn excitatory neurons in vivo: soma translocation, locomotion, and multipolar migration. Furthermore, we have identified two unique tangential migration pathways for cortical inhibitory neurons: through the marginal zone and the subventricular zone. Notably, major types of cortical inhibitory neurons, those expressing parvalbumin or somatostatin, show varied multidirectional migration patterns in the MZ and a uniform directionality in the SVZ. Our findings significantly advance the understanding of neuronal migration dynamics. We further report novel interactions between migrating inhibitory neurons and blood vessels in vivo, where neurons retract their leading processes to avoid vessels. These neurons also engage with microglia, which dynamically alter their morphology to scan and form hotspots that contribute to maintaining structural integrity under both physiological and pathological conditions. Furthermore, our findings also demonstrate that the embryonic brain rapidly mobilizes macrophages within the vasculature in response to lesions, suggesting a novel

and critical role for microglia in promoting lesion repair during embryonic brain development. Together, these results uncover distinct migration patterns of diverse neuronal types within the developing neocortex in vivo and reveal new roles for microglia in neuronal guidance and embryonic brain health maintenance.

Disclosures: Z. Long: None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.08/A21

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant EY007060
NIH Grant EY007003
NIH Grant OD011021
unrestricted grant from Research to Prevent Blindness

Title: Determining the Function of IL10 Receptor Signaling During Neuronal Regeneration in Zebrafish

Authors: P. HAGAN[1], P. F. HITCHCOCK[2], ***M. NAGASHIMA**[1];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Dept Ophthalmol, Univ. of Michigan, Ann Arbor, MI

Abstract: Zebrafish possess the ability to regenerate damaged tissues, including the heart, fins and central nervous system. In the retina, neuronal cell death ultimately results in regeneration and restoration of visual function. Regeneration of retinal neurons involves reprogramming and division of Müller glia, a radial glia common to all vertebrate retinas, and proliferation of Müller glia-derived progenitors, which differentiate into neurons. Inflammation, a universal tissue-level response to cellular damage, is required to trigger tissue regeneration in zebrafish. Interleukin-10 (Il10) is an anti-inflammatory cytokine that downregulates the expression of pro-inflammatory genes. Il10 binds to the tetrameric Il10 receptor complex, which consists of two Il10 receptor alpha and two Il10 receptor beta subunits. In the retina, the alpha subunit is expressed exclusively by microglia, the innate immune cells of the central nervous system, while the beta subunit is ubiquitously expressed. To investigate the mechanisms underlying the microglia-specific function of Il10 receptor signaling, we used CRISPR-Cas9 gene editing and created loss of function mutants for il10ra and analyzed regeneration following photolytic lesion of photoreceptors. We designed and injected guide RNAs that target 2, 3, and 4 exons of *il10ra* and successfully introduced frameshift mutations, resulting in premature stop codons and predicted truncations of the Il10ra protein. Injury-induced proliferation, neurogenesis and the response of microglia were evaluated in wildtype and mutant retinas. Immunohistochemistry for PCNA, proliferating nuclear cell antigen, at 5 dpl (days post lesion) found a significant increase in the

number of PCNA-positive cells in the *il10ra* mutants compared to wildtype. This suggests that Il10ra signaling functions to downregulate proliferation of Müller glia-derived progenitors following a lesion. At 14 dpl, there is no qualitative difference in the number and morphology of regenerated photoreceptors between wildtype and *il10ra* mutants, whereas the number of newly generated amacrine and ganglion cells was significantly increased. This suggests that Il10ra signaling also plays a role in controlling neurogenesis during regeneration. The microglial response to a lesion was evaluated using the mutant carrying microglial reporter, *il10ra*$^{-/-}$*:Tg(mpeg1.1:eGFP)*. At 5 dpl, the number of microglia in the *il10ra* mutants was marginally higher than in wildtype retinas. This result indicates that Il10ra signaling also governs the response of microglia to a retinal lesion.

Disclosures: **P. Hagan:** None. **P.F. Hitchcock:** None. **M. Nagashima:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.09/A22

Topic: A.01. Neurogenesis and Gliogenesis

Support: University Research Board at American University of Beirut (AUB)

Title: Rb predominantly compensates for the double loss of p130 and p107 in adult and embryonic neural stem cell lineages

Authors: ***R. SWAIDAN**[1], A. BEJJANI[2], A. DAHER[1], Y. E. EL ATIE[1], R. BOU HAMDAN[1], Y. CHEHAB[1], R. VANDENBOSCH[3], R. S. SLACK[4], S. OMAIS[5], N. GHANEM[1];
[1]American Univ. of Beirut, Beirut, Lebanon; [2]Cincinnati Children's Hosp. Med. Ctr., Ohio, OH; [3]Univ. of Liège, Liège, Belgium; [4]Univ. of Ottawa, Ottawa, ON, Canada; [5]Lebanese American Univ., Beirut, Lebanon

Abstract: The Retinoblastoma (Rb) family of pocket proteins is comprised of Rb, p107 and p130 that act as key cell cycle regulators to control all aspects of neurogenesis in the embryonic and adult brain. Yet, the extent to which each protein might compensate for other family members remains unclear. Adult neural stem cells (aNSCs) reside in the subventricular zone (SVZ) and the subgranular zone (SGZ) and are maintained as quiescent populations throughout life. Generation of new neurons hence depends on effective regulation of exit from quiescence and precise cell cycle control. While Rb and p107 play distinct roles during adult neurogenesis (AN), the role of p130 remains unknown. Moreover, Fong et al. 2022 recently reported that compound loss of all pocket proteins induces fast activation of aNSCs leading to pool depletion inside the SGZ. To investigate whether pocket proteins play distinct and/or synergistic roles in the SVZ, we examined here the phenotypes of embryos and adult mice carrying double and triple deletions of these proteins. We generated triple-knockout (TKO) mice that are p107 null and

carry floxed alleles for Rb and p130 as well as double-knockout (DKO) mice that have one functional Rb allele. Triple heterozygote mice (THC) were used as controls. Using a Nestin-CreERT2-YFP system, gene deletions were induced by tamoxifen injections at E10.5 and 2 months of age, and, embryos were collected at E14.5 and E17.5 while adult mice were sacrificed either 4-, 8- or 16-weeks later. Our results showed that loss of all pocket proteins during AN in the SVZ leads to: 1) exit from quiescence and fast activation of aNSCs causing pool depletion 4 months later, 2) enhanced neuroblast production and migration along the RMS, 3) massive cell death of neuroblasts prior to terminal differentiation inside the OB, and 4) remarkable shift towards astrocyte differentiation. A single Rb allele can rescue this phenotype and maintain AN as seen in DKO mice. At E14.5 and compared with controls, TKO embryos exhibit: 1) significant reduction in brain size with severe cortical lamination defects, 2) ectopic proliferation and 3) notably, premature terminal neuronal differentiation that is coupled to massive apoptosis in the telencephalon. TKO embryos die by E17.5 while DKO show a partial rescue of phenotype. Moreover, the adult versus embryonic TKO phenotypes described above are associated with distinct/opposite deregulations in the Notch-Hes signaling pathway. This study uncovers a critical role for the family of pocket proteins in controlling the proper balance between quiescence and neuronal differentiation and highlights a central role for Rb in this maintenance following loss of p107 and p130.

Disclosures: R. Swaidan: None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.10/A23

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH-1R01NS091617-06
NIH-1R01NS111220-01
Owens Family Foundation

Title: Investigating the role of Caspase-8/RIPK3 axis in the CNS development

Authors: *J. SHI[1], C. DEPPMANN[1], E. ZUNDER[2], A. SONG[1], T. SANNI[1];
[1]Univ. of Virginia, Charlottesville, VA; [2]Biomed. Engin., Univ. of Virgina, Charlottesville, VA

Abstract: The development of the Central Nervous System (CNS) is governed by tightly regulated processes critical for the proper formation and refinement of neural networks. Among these mechanisms, regulated cell death (RCD), encompassing forms including apoptosis and necroptosis, serves as a major regressive event that sculpts the CNS by eliminating excess cells, thereby maintaining tissue integrity and circuitry functionality. Disruptions in RCD have been implicated in various neurodevelopmental and neurodegenerative disorders. Despite their

significance, the precise contribution of distinct cell death pathways remains unclear, hindering our understanding of fundamental principles governing cell fate. Our study investigates the contributions of extrinsic apoptosis and necroptosis, particularly focusing on the pivotal role of Caspase-8 and RIPK3, in CNS development. *Rationale:* Caspase-8 plays multiple roles, including activating the extrinsic pathway of apoptosis and inhibiting necroptosis via RIPK1 interaction. The balance between extrinsic apoptosis and necroptosis significantly influences cellular outcomes. Despite the known importance of Caspase-8 and RIPK3, their precise contributions, especially regarding cell abundance in CNS, remain poorly defined. *Approach:* We collected microdisected telencephalon tissue from P0 and P4 RIPK3$^{-/-}$, RIPK3$^{-/-}$Casp8$^{-/-}$ (DKO), and C57/BL6 (WT) mice for mass cytometry analysis. Additionally, immunohistochemistry on brain slices was performed to validate cytometry findings, focusing on neuronal and endothelial densities. *Results:* Compared to WT and RIPK3$^{-/-}$ mice, DKO mice showed significantly increased abundance of endothelial cells and Tbr2-high neurons, suggesting the involvement of extrinsic apoptosis in sculpting these cell populations. Additionally, the loss of extrinsic apoptosis and necroptosis may trigger compensatory cell death mechanisms. *Conclusion:* Our findings shed light on the distinct roles of extrinsic apoptosis and necroptosis in CNS development, highlighting the significance of Caspase-8 and RIPK3 in regulating cellular abundance. A deeper understanding of these pathways enhances our comprehension of CNS development and may offer insights into novel drug targets of neurodevelopmental disorders.

Disclosures: J. Shi: None. **C. Deppmann:** None. **E. Zunder:** None. **A. Song:** None. **T. Sanni:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.11/A24

Topic: A.01. Neurogenesis and Gliogenesis

Title: Label-free 3d high-resolution imaging of live primary neuronal cells and fixed mouse brain structures using low-coherence holotomography

Authors: H. HOANG[1], ***H.-Y. KANG**[1], H.-J. KIM[1], J. LEE[1], H. LEE[1], M. KIM[1], H. TRAN[1], S. LEE[1], Y. PARK[2];
[1]Tomocube, Inc., Daejeon, Korea, Republic of; [2]KAIST, Daejeon, Korea, Republic of

Abstract: Recent advances in imaging technologies have revolutionized our understanding of nervous system architecture and function. Low-coherence holotomography (HT) is a promising label-free method for three-dimensional (3D) visualization of biological specimens, relying on refractive index (RI) distributions. By taking advantage of this, capturing the spatial and temporal dynamics of neurons and their networks provides clues for understanding the complex nature of the neuronal network system. Here, HT addressed challenges of structural delineating

of brain tissue sections and the longitudinal tracking of neuron cell behavior. This study reveals detailed spatial features of mouse brain tissue sections, such as the hippocampus and the Paraventricular Nucleus of Thalamus (PVT), at single-axon resolution, facilitating precise sample identification. For longitudinal assessment, primary rat neuron cells were monitored over 12 hours at 2-minute intervals using HT without labeling. Observations included axon elongation guided by growth cones, antero-/retrograde mitochondrial transport within the axon, and the emergence of dendritic spines, challenging to observe with standard techniques due to size and rapid movements. HT's exceptional spatial and temporal resolution enables observation of these fine structures within the natural state of the nervous system. HT's high-resolution, label-free visualization of living neurons and brain tissue holds promise for advancing basic and translational neuroscience. Unlike traditional staining methods, HT allows non-destructive assessment of neuronal development and pathologies, offering clarity in observing neuronal networks. Time-lapse HT imaging of neuronal growth cones provides insight into network formation and regeneration, with implications for neurodegenerative disease treatment and understanding neuronal network-behavioral relationships. This innovative approach enhances our understanding of neuroscience principles and holds significant potential for clinical neurology, facilitating improved diagnostic tools and treatment strategies for neurological disorders.

Disclosures: H. Hoang: A. Employment/Salary (full or part-time):; Tomocube, Inc. **H. Kang:** A. Employment/Salary (full or part-time):; Tomocube, Inc. **H. Kim:** A. Employment/Salary (full or part-time):; Tomocube, Inc. **J. Lee:** A. Employment/Salary (full or part-time):; Tomocube, Inc. **H. Lee:** A. Employment/Salary (full or part-time):; Tomocube, Inc. **M. Kim:** A. Employment/Salary (full or part-time):; Tomocube, Inc. **H. Tran:** A. Employment/Salary (full or part-time):; Tomocube, Inc. **S. Lee:** A. Employment/Salary (full or part-time):; Tomocube, Inc. **Y. park:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tomocube, Inc..

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.12/A25

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSERC RGPIN-2019-04533

Title: Colony stimulating factor-1 receptor signaling as a regulator of developmental microglial proliferation

Authors: *B. P. HAMMOND[1], E. HAHN[2], S. FRIESEN[3], T. LANGE[2], F. BRETHEAU[4], A. CASTELLANOS MOLINA[5], S. LACROIX[6], J. R. PLEMEL[7];
[1]Neurosci. and Mental Hlth. Inst., Univ. of Alberta, Edmonton, AB, Canada; [2]Univ. of Alberta,

Edmonton, AB, Canada; [3]Biol. Sci., Univ. of Alberta, Edmonton, AB, Canada; [4]Univ. Laval, Quebec, QC, Canada; [5]Ctr. de recherche CHU de Québec-Université Laval, Québec, QC, Canada; [6]Mol. Med., Univ. Laval, Quebec, QC, Canada; [7]Dept. of Med., Div. of Neurol., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Microglia—the immune sentinels of the central nervous system—display a remarkable capacity for proliferation in murine development. Such developmental proliferation establishes an adulthood microglial population that, at homeostasis, remains at a stable density and is minimally proliferative. However, the factors that regulate developmental microglial proliferation remain unknown. In our work, we histologically confirmed that developmental proliferation of microglia is restricted to the first two postnatal weeks and is minimal in adulthood. This suggests that there is a cue, or set of cues, that instruct developmental microglial proliferation in a temporally restricted manner. To explore the factors that might promote this proliferation, we treated serum-free microglial cultures with several factors previously suggested to regulate microglial population dynamics. Of these, only four factors directly boosted microglial proliferation: colony stimulating factor (CSF)-1, interleukin (IL)-34, CSF-2 and IL-3. To explore these factors as potential regulators of developmental proliferation, we assessed the expression of each at the transcriptional level in the developing brain using RNAscope. We found only *Csf1* and *Il34* were expressed in the developing brain. Interestingly, both CSF-1 and IL-34 share the colony-stimulating factor-1 receptor, which is specific to microglia and a few border-associated macrophages in the developing brain. At the transcriptional level, we found that *Csf1* and *Il34* were expressed in distinct spatial and temporal patterns. Similarly, we used an enzyme-linked immunosorbent assay to verify that both CSF-1 and IL-34 expression increase during development, alongside microglial proliferation. To identify the cell lineages that may express these two factors, we are currently using a combinatorial approach of bioinformatic analyses of publicly available datasets and fluorescent immunohistochemistry. With this study, we are beginning to dissect the mechanisms responsible for developmental microglial proliferation—a critical process for appropriate neurodevelopment.

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Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.13/A26

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01AI147496
1S10OD028515-01

Title: Effect of ethanolamine phospholipid deficiency on oligodendrocyte precursor cell proliferation and differentiation

Authors: *L. A. NUNES[1], C. MA[2], F. HOFFMANN[2], M. W. PITTS[2], P. HOFFMANN[2];
[1]Anatomy, Biochemistry, and Physiol., [2]Cell and Mol. Biol., Univ. of Hawaii, Honolulu, HI

Abstract: Selenoprotein I (SELENOI; EPT1) is an endoplasmic reticulum resident ethanolamine phosphotransferase that catalyzes the final reaction of the ethanolamine branch of the Kennedy Pathway of phospholipid synthesis, in which phosphatidylethanolamine (PE) and plasmenyl PE are produced. PE is a major component in mammalian cellular membranes and plays a key role in membrane architecture while also serving as a precursor for biologically active molecules. Plasmenyl PE is enriched in nervous tissues, particularly in myelin, serving a critical role in a variety of biological functions including neuroprotection through scavenging reactive oxygen species (ROS). Rare mutations in SELENOI have been shown to be associated with a complex form of hereditary spastic paraplegia (HSP). HSP, a large group of neurodevelopmental and/or neurodegenerative disorders of multigenetic origin, results in spasticity and weakness in the lower limbs. Patients deficient of SELENOI suffer from a myriad of debilitating symptoms including severely delayed growth, cerebral and cerebellar atrophy, delayed motor development, lower limb spasticity, and hypomyelination. We developed a murine nervous system specific conditional knockout of SELENOI (Tuba1a-Cre:SELENOI FL/FL) and observed profound deficits in rotarod and vertical pole tests of motor coordination accompanied by hypomyelination and reactive gliosis in regions of the corticospinal tract. Furthermore, lipidomic and flow cytometric analyses of whole brains revealed altered lipid profile, elevated lipid peroxidation, and reduced percentage of myelinating oligodendrocytes. These findings suggested that cells of the oligodendroglial lineage are most vulnerable to the loss of SELENOI. During proliferation and differentiation, oligodendrocyte progenitor cells (OPC) require the uptake of large amounts of iron. This accumulation of ferrous iron, however, leads to the increased production of ROS, which can oxidize lipid species. The intracellular accumulation of iron and lipid oxidation are two hallmarks of ferroptosis, a non-apoptotic cell death pathway. We hypothesize that loss of SELENOI in OPCs results in increased vulnerability to lipid peroxidation and a compensatory reduction in iron uptake to prevent ferroptosis. Mixed cortical cultures from Tuba1a-Cre:SELENOI FL/FL mice confirmed the reduction in mature oligodendrocyte frequency and revealed altered iron uptake *ex vivo*. Subsequently, we isolated OPCs and evaluated their proliferation and differentiation capacities, vulnerability to cell death inducers, and iron and lipid peroxidation levels.

Disclosures: L.A. Nunes: None. **C. Ma:** None. **F. Hoffmann:** None. **M.W. Pitts:** None. **P. Hoffmann:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.14/A27

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH EY031690

Title: Protocadherin γC4 promotes neuronal survival in the mouse retina

Authors: *C. MCLEOD[1,2], S. BHANDARI[2], A. M. GARRETT[2];
[2]Pharmacol., [1]Wayne State Univ., Detroit, MI

Abstract: During the first two postnatal weeks of life a massive wave of programmed cell death refines and shapes the developing CNS. During this critical period, a neuron's choice between survival and death via apoptosis is finely regulated, with errors in number and population of neurons resulting in neural circuit dysfunction. As circuit dysfunction is associated with a range of neurodevelopmental disorders; it is essential to understand the molecular cues that govern neuronal survival. The gamma-protocadherin gene cluster (*Pcdhg*) encodes for 22 homotypic cell adhesion molecules, where each protein consists of six distinct extracellular cadherin like domains, and a short variable cytoplasmic region, but all isoforms share an identical intracellular C-terminal constant domain. Among these isoforms, protocadherin γC4 has been shown to promote neuronal survival in the mouse CNS, where its absence results in a massive exacerbation of normal developmental apoptosis in interneurons and is lethal within hours after birth. How the expression of this one isoform is able to serve as a survival cue in some neuronal populations, while the other 21 highly similar Pcdhg isoforms cannot, remains unclear. To this end, we use the mouse retina as a model system to explore the mechanics behind γC4 mediated neuronal survival. Using RNAscope, we found that the neuronal expression of γC4 during development is correlated with the reliance of a given neuronal subtype on γC4 for survival. We are currently using live cell imaging to map the protein domains of γC4 that are essential for survival, by rescuing apoptosis with a series of truncated and domain swapped constructs in mutant $Pcdhg^{C4KO/C4KO}$ retina cultures. We are also using a proteomics approach with tissue from γC4 transgenic animals to identify binding partners unique to this isoform that may be involved in programmed cell death. Taken together these data reveal what makes γC4 unique among Pcdhg isoforms and may suggest a starting point for understanding where γC4 intervenes in the process of programmed cell death during neurodevelopment.

Disclosures: C. McLeod: None. **S. Bhandari:** None. **A.M. Garrett:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.15/A28

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R01-NS115400

Title: The F-BAR proteins CIP4 and FBP17 regulate neurite dynamics during cortical neuronal migration

Authors: *L. A. ENGLISH[1], R. J. TAYLOR[2], C. J. CAMERON[2], E. A. BROKER[2], E. W. DENT[2];
[1]Univ. of Wisconsin - Madison Neurosci. Training Program, Madison, WI; [2]Neurosci., Univ. of Wisconsin - Madison, Madison, WI

Abstract: Neurite initiation from newly born neurons is a critical step in neuronal differentiation and migration. Additionally, neuronal migration in the developing cortex is accompanied by dynamic extension and retraction of neurites as neurons progress through bipolar and multipolar states. However, there is a relative lack of understanding regarding how the dynamic extension and retraction of neurites is regulated during neuronal migration. In recent work we have shown that CIP4, a member of the F-BAR family of membrane bending proteins, inhibits cortical neurite formation in culture, while family member FBP17 induces premature neurite outgrowth. These results beg the question of how CIP4 and FBP17 function in radial neuron migration and differentiation *in vivo*, including the timing and manner of neurite repression. To examine the effects of modulating expression of CIP4 and FBP17 *in vivo*, we used *in utero* electroporation, in combination with our published Double UP technique, to allow for comparison of experimental (knockdown or overexpression) and control cells within the same tissue. We show that either knockdown or overexpression of CIP4 and FBP17 results in the marked disruption of radial neuron migration by modulating neurite outgrowth. The regulation of neurite outgrowth is essential to the shifts between bipolar and multipolar states during radial migration. Our results demonstrate of F-BAR proteins may regulate neurite initiation during cortical neuronal migration.

Disclosures: L.A. English: None. **R.J. Taylor:** None. **C.J. Cameron:** None. **E.A. Broker:** None. **E.W. Dent:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

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Program #/Poster #: PSTR002.16/A29

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIGMS DP2 GM137423
NIMH R01 MH130594
SFARI Pilot Award (615098)

Title: Alternative splicing of transcription regulators in the developing neocortex

Authors: *X. RUAN[1], K. HU[2], Y. YANG[2], R. YANG[2], X. ZHANG[2];
[1]Univ. of Chicago, CHICAGO, IL; [2]Human Genet., Univ. of Chicago, Chicago, IL

Abstract: How master splicing regulators crosstalk with each other and to what extent transcription regulators are differentially spliced remain unclear in the developing brain. Here, cell-type-specific short- and long-read RNA-Seq of the developing neocortex uncover that transcription regulators are enriched for differential splicing, altering protein isoforms or inducing nonsense-mediated mRNA decay. Transient expression of Rbfox proteins in radial glia progenitors induces neuronal splicing events preferentially in transcription regulators such as Meis2 and Tead1. Surprisingly, Rbfox proteins promote the inclusion of the Ptbp1 mammal-specific alternative exon and a previously undescribed poison exon. Simultaneous ablation of Rbfox1/2/3 in the neocortex increases progenitor cell-enriched isoforms and disrupts radial neuronal migration. Furthermore, the progenitor isoform of Meis2 promotes Tgfb3 transcription, while the Meis2 neuron isoform promotes neuronal differentiation. These observations indicate transcription regulators are differentially spliced between cell types in the developing neocortex.

Disclosures: **X. Ruan:** None. **K. Hu:** None. **Y. Yang:** None. **R. Yang:** None. **X. Zhang:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.17/A30

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01NS100514

Title: Age-related changes in glial progenitor proliferation kinetics in the rat entorhinal cortex in the presence or absence of trophic factor stimulation

Authors: J. YOUSEY, ***D. A. PETERSON**;
Rosalind Franklin Univ. Med. Sci., North Chicago, IL

Abstract: While the neurogenic niches are spatially restricted, the adult brain does contain a widespread population of glial progenitor cells that are committed to the oligodendrocyte lineage called oligodendrocyte progenitor or precursor cells (OPCs). These cells are highly proliferative and maintain a uniform distribution matrix throughout gray and white matter. We have recently shown that OPCs resident in the cortex of young adult rats can be reprogrammed into neurons. We used retroviral delivery of reprogramming factors to specifically target proliferating OPCs in the young adult rat cortex. To approach the goal of targeting OPCs in the aged cortex for reprogramming, we began by investigating their proliferation characteristics as a function of age. In agreement with a previous study of aging-related changes from embryonic through mid-adult ages in a mouse model, we found a significant drop in proliferating cells in aged rat entorhinal cortex. We chose to focus on entorhinal cortex (ECX), due to its relevance for age-related neurodegenerative disease and its important role in learning and memory. Although the age-related decline in proliferation was striking, the recently generated cell populations remained

stable over time. To investigate the phenotype of the proliferative population, we assessed their co-expression of markers for neurons (NeuN), astrocytes (GFAP), microglia (Iba1) and OPCs (NG2). While the occasional BrdU+/GFAP+ or BrdU+/Iba1+ cell was observed, nearly all of the proliferating cells were NG2+ OPCs. However, with an increasing post-mitotic interval, the proportion of cells continuing to express NG2 declined. This loss of NG2 was particularly observed in the aged ECX. We expect that the loss of NG2 expression represents the lineage progression from NG2-expressing OPCs to pre-oligodendrocytes and terminally differentiated oligodendrocytes. We next asked if OPC proliferation in young and aged ECX could be stimulated following in vivo gene delivery of FGF-2 or BDNF. While both FGF-2 and BDNF significantly elevated proliferation in the young ECX, only FGF-2 significantly elevated proliferation in the aged ECX. These results show that, although reduced with aging, cortical OPCs continue to proliferate and are responsive to some trophic signals. This suggests it may be possible to stimulate the expansion of the OPC population in aged cortex as a prelude to gene delivery of neuronal reprogramming factors.

Disclosures: J. Yousey: None. **D.A. Peterson:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.18/A31

Topic: A.01. Neurogenesis and Gliogenesis

Title: Traffic-related air pollutants induce neuroinflammation and early mortality

Authors: B. MCGUIRE, *P. PERSAUD, S. GUARIGLIA;
New York State Inst. for Basic Res., Staten Island, NY

Abstract: Traffic-related air pollutants have garnered attention due to their harmful effects on human health. Proximity to highways has been associated with detrimental impacts on neurodevelopment, increasing the risk of Autism Spectrum Disorders (ASD). Vehicles emit various pollutants into the atmosphere, ranging from carbon monoxide and dioxide to nitrogen oxides, sulfur oxides, volatile organic compounds, and polycyclic aromatic hydrocarbons (PAHs). These pollutants undergo chemical reactions, giving rise to secondary pollutants such as fine particulate matter (PM2.5) and ozone. Exposure to these pollutants has been linked to inflammation, which poses a significant threat to neurodevelopmental processes. Thus, our study assesses the effects of a PAH mixture representative of New York City air and ozone on microglial activation, astrocyte proliferation, and overall neuroinflammation. To conduct our investigation, embryonic zebrafish (Danio rerio) were exposed to varying concentrations of PAH solutions, which included 0 ppm (control), 0.1 ppm (low), 1 ppm (middle) and 10 ppm (high). A second group was exposed to ozonated water 0 ppm (control), 0.05 ppm (low), 0.5 ppm (middle) and 5 ppm (high). Exposures started 24 hours post fertilization (HPF) and continued until 72 hpf,

which is the point at which they hatch. At 144 hours hpf, we quantified GFAP, a marker for astrocytes, IbA, a marker for microglia, and TSPO, a marker for neuroinflammation, in the zebrafish tectum using Western Blot and Immunohistochemistry. Our results revealed a significant increase in GFAP, IbA, and TSPO levels following middle-level exposures. High-level exposures led to the death of more than 50% of developing embryos (LD50). Immunohistochemical analysis of the tectum provided evidence of astrocytic aggregates, which were further confirmed through electron microscopy. The combination of both PAH and Ozone middle doses exacerbated GFAP, IbA, and TSPO expression without resulting in any significant change in survivorship. Additionally, zebrafish exposed to any pollutant level did not survive beyond 14 days of development, highlighting the persistence of developmental changes induced by these pollutants that ultimately result in early mortality. Collectively, our data demonstrates that even transient exposure to traffic-related air pollutants induces neuroinflammation and persistent alterations in overall development, culminating in early mortality. Our study underscores the critical need to address the adverse impacts of traffic-related air pollutants on development and neurodevelopment.

Disclosures: B. McGuire: None. **P. Persaud:** None. **S. Guariglia:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

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Program #/Poster #: PSTR002.19/A32

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH/NIMH Grant R01MH132018-02
NSF Grant IOS 2137023

Title: Cortical lamination and sociocognitive behavior in mice exposed to organophosphatesin utero.

Authors: *T. VAUGHN[1], A. VATS[1], T. T. ADEYELU[2], O. M. OGUNDELE[1];
[1]Louisiana State Univ., Baton Rouge, LA; [2]Comparative Biomed. Sci., Louisiana State Univ., Baton Rouge, LA

Abstract: Organophosphates are chemicals used in pesticides, and other domestic or industrial reagents. Because of their broad applications in household, industrial, and farm processes organophosphates can contaminate food and water sources. It is well established that maternal exposure to environmental toxins, including organophosphates, leads to cognitive and social behavioral defects in offspring. To explore the impact of prenatal organophosphate exposure on socio-cognitive function during postnatal developmental stages and brain growth and development. This study investigates how in utero exposure to commonly used organophosphates, or organophosphate mixtures can cause neurological disorders by impairing

neuronal migration and cortical organization. C57BL/6 mice (1 male/ 2 female) were paired for mating, and the female mice were monitored for gestation. Vaginal smears were preformed to detect ovulation and onset of pregnancy. Present of vaginal plug indicated gestational day zero (GD). In utero exposure was achieved by oral administration of organophosphate to pregnant female mice between GD7-GD14. Two different concentrations of organophosphate compounds were administered to separate sets of pregnant mice (i) chlorpyrifos high concentration (6mg/kg), (ii) chlorpyrifos low concentration (3mg/kg). Control mice received the diluent (corn oil in water) from GD 7 to GD 14. Treatment and control pups were euthanized on P0. Brains were processed for immunofluorescence to label cortical neurons in the upper layers (Cux1, layers II-IV) and lower cortical layers (Tbr1, layer V-VI). This will allow us to ascertain the distribution of neurons within the layers of the prefrontal cortex. Here, we will determine whether organophosphates induce erroneous migration, or delayed the migration of neurons within the cortical layers. Additional layer-specific labeling will be performed pending the outcome of *Cux1*$^+$ and *Tbr1*$^+$ neuron distribution analysis. We will also assess the expression of proteins associated with cytoskeletal assembly and axon guidance in the cortex of mice exposed in utero to organophosphates. Specifically, western blotting will be performed to detect GSK3*β, TKR, PI3K, AChE, LRp6, Tubulin, Ephrin/Eph, Slit/Robo*. Completing these experiments will allow us to determine how organophosphate might affect axon guidance and cortical lamination in the developing brain. Keywords**:** organophosphates, Neuronal-migration, immunofluorescence

Disclosures: T. Vaughn: None. **A. Vats:** None. **T.T. Adeyelu:** None. **O.M. Ogundele:** None.

Poster

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Topic: A.01. Neurogenesis and Gliogenesis

Support: PID2020-118171RB-I00
PROMETEO CIPROM/2021/018
RD21/0017/0017
The Walk on Project

Title: Investigating the impact of Lis1 Mutation on the development of Somatostatin+ Interneurons in the Cingulate Cortex

Authors: *A. POMBERO[1], R. GARCIA-LOPEZ[2], E. GEIJO-BARRIENTOS[3], S. MARTINEZ[4,5,6];
[1]Inst. De Neurociencias, San Juan De Alicante, Spain; [2]Inst. Neurociencias, San Juan De Alicante, Spain; [3]Univ. Miguel Hernandez-CSIC, San Juan, Alicante,, Spain; [4]Inst. de Neurociencias, Inst. De Neurociencias. UMH-CISC, San Juan De Alicante, Spain; [5]Ctr. de

Investigación Biomédica En Red en Salud Mental-CIBERSAM-ISCIII, Valencia, Spain; [6]Inst. de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, Spain

Abstract: Approximately a quarter of all neurons are inhibitory interneurons, among which somatostatin-positive interneurons (SST+ interneurons) constitute a distinct subtype expressing both somatostatin and GABA. These cells play a crucial role in modulating cortical information processing and maintaining excitation/inhibition balance by forming synapses with pyramidal neurons and other interneurons. Originating from the medial ganglionic eminence, SST+ interneurons follow a tangential pathway to the cortex, rendering them susceptible to gene mutations affecting neuronal migration. Platelet-activating factor acetylhydrolase 1B subunit alpha (Pafah1b1 or Lis1), a gene regulating various cellular processes, is associated with lissencephaly in humans and disrupts neural migration, leading to cortical and hippocampal disorganization, spatial learning deficits, epilepsy, and excitation/inhibition imbalances. To investigate Lis1's role in SST+ interneurons, we developed a novel animal model with Lis1 gene deletion specifically in SST+ interneurons. Our study focused on examining the anatomical and developmental consequences of Lis1 deficiency using stereology to assess SST+ interneuron populations in the cingulate cortex at postnatal stages (P15 and P30). Additionally, we analyzed potential disruptions in tangential migration during embryonic development (E14.5 and E16.5). Our findings revealed a decrease in SST+ interneurons in the cingulate cortex of mutant mice, along with reduced migrating interneurons expressing SST in the developing cortex, suggesting Lis1's involvement in SST+ interneuron development. Further research is warranted to elucidate the underlying mechanisms driving this reduction and its functional implications.

Disclosures: A. Pombero: None. **R. Garcia-Lopez:** None. **E. Geijo-Barrientos:** None. **S. Martinez:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.21/A34

Topic: A.01. Neurogenesis and Gliogenesis

Support: PID2020-118171RB-I00
PROMETEO CIPROM/2021/018
The Walk on Project
RD21/0017/0017

Title: The Potential contribution of fibroblast growth factor receptor 1 (Fgfr1) to retrosplenial cortex development.

Authors: *R. GARCIA-LOPEZ[1], A. POMBERO[2], S. MARTINEZ[3,4,5];
[1]Inst. Neurociencias, San Juan De Alicante, Spain; [2]Inst. De Neurociencias, San Juan De

Alicante, Spain; [3]Inst. de Neurociencias, Inst. De Neurociencias. UMH-CISC, San Juan De Alicante, Spain; [4]Centro de Investigación Biomédica En Red en Salud Mental-CIBERSAM-ISCIII, Valencia, Spain; [5]Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, Spain

Abstract: The retrosplenial cortex (RSP) is situated in the medial and caudal regions of the brain, bridging the neocortex and the archicortex. As an integral component of the limbic circuit, this cortical area plays a crucial role in various cognitive functions, including emotion regulation, attention, and spatial memory. Its intricate network of connections encompasses the anterior and dorsomedial thalamic nuclei, the hippocampal formation, the amygdaloid complex, and extensive neocortical areas. Implicated in the pathophysiology of schizophrenia, both human studies and animal models have linked hyperactive behavior to aberrations in the RSP.Fibroblast growth factors (FGFs) and their receptors (FGFRs) are pivotal in the development and maintenance of the central nervous system. They orchestrate the morphogenesis of the mammalian cerebral cortex, with Fgfr1 gene expression notable in the dorsal ventricular zone (VZ) during cortical primordium development, as well as in the upper layers of the RSP cortex during postnatal stages (as evidenced by the Allen Brain Atlas). Previous research has shown that disruption of the Fgfr1 gene results in decreased cortical interneurons, a reduction of pyramidal neurons in frontal and temporal cortical areas, and locomotor hyperactivity.To elucidate the role of Fgfr1 in RSP development, we conditionally inactivated Fgfr1 in neuroepithelial cells of the central nervous system (Fgfr1f/f;NesCre+). Our analyses, encompassing volume estimation of cortical layers and quantification of pyramidal neurons and parvalbumin-positive interneurons in the RSP, suggest that the proper formation of the RSP relies on the functional integrity of Fgfr1.

Disclosures: R. Garcia-Lopez: None. **A. Pombero:** None. **S. Martinez:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.22/A35

Topic: A.01. Neurogenesis and Gliogenesis

Support: MCIN grant-PID2020-118171RB-I00
GVA-Prometeo Grant-CIPROM/2021/018

Title: Specific effects of Lis1 mutation on the parvalbumin-positive interneurons development

Authors: *P. MADRIGAL, A. ANDREU-CERVERA, E. GEIJO-BARRIENTOS, S. MARTINEZ;
UMH, Alicante, Spain

Abstract: Many brain pathologies exhibit an imbalance between excitatory and inhibitory actions within brain microcircuits. The loss or dysfunction of parvalbumin-positive interneurons (PV+), a subtype of interneurons, is associated with network disruption and cognitive impairments in various neuro-psychiatric disorders. Platelet-activating factor acetylhydrolase 1B subunit alpha (known as Lis1) is a regulator of dynein mediated motility, mitosis nuclear positioning, and microtubule organization. *Lis1* gene mutation has been linked to lissencephaly, neural migration defects, and epilepsy in humans. To study the role of *Lis1* in interneurons, we have developed an animal model with specific Lis1 gene deletion in PV+ interneurons. We focused on anatomical consequences of Lis1 silencing. Firstly, we have studied the PV+ interneurons density in the cingulate cortex (ACC, cingulate anterior and RSP, retrosplenial cortices). Our results show a PV+ interneurons reduction in the ACC (48%) of mutant mice compared to controls in cortical layers II/III, V and VI, and a reduction in agranular part of the RSP (52%) in the same cortical layers at P21. However, this reduction is not shown at P15 cortex. Therefore, this result suggests a possible alteration of cell apoptosis in the cingular cortex in the time window between P15 and P21. Moreover, we also explored the possible alteration in their activity, using cFos as an activity marker by three-dimensional immunohistochemistry (iDSICO protocol) to explore the whole brain postnatally. Our results indicate an increase of $cFos^{+}/PV^{-}$ cells at different cerebral regions, including cingular cortex (ACC, RSP) and other extra-cortical areas such as paraventricular nucleus, a specific hypothalamic nucleus. More experiments will be necessary to understand the underlying mechanisms of this effects, as well as to evaluate the functional consequences derived from these alterations. Research supported by MCIN grant-PID2020-118171RB-I00, GVA-Prometeo Grant-CIPROM/2021/018.

Disclosures: P. Madrigal: None. **A. Andreu-Cervera:** None. **E. Geijo-Barrientos:** None. **S. Martinez:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.23/A36

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS082174

Title: Visualization of ocular motor neuron subpopulations during development

Authors: *S. A. SANTOS[1], N. SHIROONI[1], M. F. ROSE[2];
[1]Univ. of California Irvine, Irvine, CA; [2]Pathology and Lab. Med., Univ. of California Irvine, Irvine, CA

Abstract: Motor neuron development involves cell proliferation, specification, and migration in the central nervous system and axon targeting to specific muscles in the periphery. A subset of

the brainstem oculomotor neurons (cranial nucleus 3, CN3), which control eye movement, migrate across the midline in a rare process. This subpopulation is selectively vulnerable in the childhood neurologic disease “Congenital fibrosis of the extraocular muscles type 1” (CFEOM1), where mutations in the kinesin KIF21A cause axon stalling and resulting deficits in upward gaze. The unique genes that direct each of these processes in the various motor neuron types and subpopulations, and their contributions to selective vulnerability in disease remain to be fully defined. We have adapted an ex vivo slice culture live imaging platform to visualize motor neuron development at single cell resolution. We use a combination of in vivo mouse genetic reporters to label the motor neurons, including the transgene Isl1-GFP and Cre lines such as Phox2b-cre and Isl1-cre in combination with the fluorescent cre reporter ROSA-tdTomato. We plan to intersect these tools and tissue clearing approaches to visualize motor neuron processes both during normal development and in disease models. In addition, we and colleagues have generated an atlas of developing motor neuron gene expression from which we have identified candidate genes of CN3 motor neuron subpopulations during differentiation. To determine the extent to which the candidate genes are critical for ocular motor neuron development, we will disrupt their expression using CRISPR-Cas9, followed by analysis with our imaging pipeline. Overall, visualization of the dynamic behaviors among the CN3 motor neuron subpopulations and their progenitors will better define their population-specific choices during development and selective vulnerability in disease, and clarify the timing and function of gene expression that could inform future regeneration protocols.

Disclosures: **S.A. Santos:** None. **N. Shirooni:** None. **M.F. Rose:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.24/A37

Topic: A.01. Neurogenesis and Gliogenesis

Title: Building a gene expression atlas of developing brainstem motor neurons as a toolbox to study rare congenital neurologic disorders.

Authors: *N. SHIROONI[1], A. TENNEY[2], A. GELBER[3], F. CHEN[4], E. ENGLE[5], M. F. ROSE[6];
[1]Univ. of California, Irvine, Irvine, CA; [2]Boston Children's Hosp., Boston, MA; [3]Bioengineering, UCSD, San Diego, CA; [4]Broad Inst., Boston, MA; [5]Neurol. Res. - Engle Lab., Boston Children's Hosp. / Harvard Med. Sch. / HHMI, Chestnut Hill, MA; [6]Pathology and Lab. Med., Univ. of California Irvine, Irvine, CA

Abstract: Ocular motor neurons (OMNs) in the brainstem mediate eye movement and are differentially affected in some rare congenital neurologic diseases. In cases such as Duane Syndrome, specific OMN subpopulations show disrupted or aberrant innervation while other

subpopulations remain unaffected, but mechanisms underlying differential susceptibilities have not yet been identified. Here we generate a transcriptomic atlas to analyze unique gene expression patterns of each developing MN type as a toolbox to help study these disorders. We combined multiple mouse genetic reporter lines with intersectional temporal (embryonic days E9.5 to E18.5) and spatial transcriptomics (single cell/nuclei RNA-seq, and Slide-Seq) to isolate and compare eight distinct mouse MN populations: the three oculomotor nuclei (CN3, CN4, CN6) and the other primary MN types (CN5, CN7, CN9/10, CN12 and spinal MNs). Sample integration posed a significant "batch effect" challenge since different types of samples were acquired via multiple methods over many ages. We compared multiple benchmarked high quality integration pipelines to balance batch correction vs. bioconservation. Once cells were identified and labeled we used scDREAMER-SUP, a semi-supervised deep learning algorithm, using cell label annotations as a means to achieve further bioconservation and batch correction. We built a visualization tool to investigate integration quality. Cell clusters were mapped onto spatial transcriptomic slide-seq samples from E11.5 and E14.5 and compared with developmental mouse atlases to confirm cell identities. Candidate marker genes of each cell population were further validated via database analysis and RNA in situ hybridization. We successfully integrated a developmental time course of mouse MN gene expression from disparate sample types. The resulting atlas can be transposed to label and identify spatial structures within slide-seq datasets to identify cells in time and space. Overall, this atlas uncovers distinct developmental gene expression patterns and provides new tools to study their differential vulnerability in motor neuron related disorders.

Disclosures: **N. Shirooni:** None. **A. Tenney:** None. **A. Gelber:** None. **F. Chen:** None. **E. Engle:** None. **M.F. Rose:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.25/A38

Topic: A.10. Development and Evolution

Support: NIH grant 1RF1MH128778
NIH grant U01MH114812
NIH grant UM1MH130981

Title: Postnatal developmental regulation of the morphoelectric properties of Human cortical neurons

Authors: K. NASIROVA[1], K. BLAKE[1], R. DALLEY[2], S. WALLING-BELL[2], N. DEE[2], S. A. SORENSEN[1], T. JARSKY[2], H. GOLDSTEIN[3], J. HAUPTMAN[3], J. OJEMANN[3], H. ZENG[2], J. T. TING[4], E. LEIN[4], B. E. KALMBACH[4], ***B. R. LEE**[1];

[1]Allen Inst., Seattle, WA; [2]Allen Inst. for Brain Sci., Seattle, WA; [3]Seattle Children's Hosp., Seattle, WA; [4]Human Cell Types, Allen Inst. For Brain Sci., Seattle, WA

Abstract: Humans undergo a prolonged postnatal development that spans distinct phases ranging from infancy, toddler, childhood, adolescence, and into adulthood. The complex interplay between cell types from neurogenesis through synaptic pruning in mature circuits involves diverse neuron types that each play a critical role. Due to recent advances in single-cell RNA-sequencing, we are beginning to understand the molecular framework of neurons through these critical timepoints. However, a deeper understanding of the corresponding phenotypic properties and circuit dynamics is lacking. Intrinsic membrane properties are crucial for defining circuit dynamics and regulating synaptic plasticity. It is hypothesized that they may change along the development trajectory. We performed Patch-seq experiments in *ex vivo* brain slices obtained from neurosurgical tissue from patients 6 weeks old through adulthood. Furthermore, we used rapid viral labeling and enhancer-based AAVs to target neurons in a cell-type specific manner. We identified putative glutamatergic and GABAergic neurons based on their transcriptome, physiology and local morphology and found that core features of subclass types were more diverse and had more variance in the infant stage (0 - 12 months) than any other time point. Gaining a deeper understanding of the phenotypic properties of cortical neurons during development will provide critical insights into neural circuitry and connectivity, cognitive function and disease.

Disclosures: K. Nasirova: None. **K. Blake:** None. **R. Dalley:** None. **S. Walling-Bell:** None. **N. Dee:** None. **S.A. Sorensen:** None. **T. Jarsky:** None. **H. Goldstein:** None. **J. Hauptman:** None. **J. Ojemann:** None. **H. Zeng:** None. **J.T. Ting:** None. **E. Lein:** None. **B.E. Kalmbach:** None. **B.R. Lee:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.26/A39

Topic: A.10. Development and Evolution

Support: R01NS123959

Title: Patch-seq reveals cell type and regional differences in subthreshold oscillations and spiking regularity in the primate neocortex.

Authors: *S. D. SAWCHUK[1], C. RADAELLI[2], X. OPITZ-ARAYA[2], J. T. TING[2], W. J. SPAIN[3], M. HUDSON[4], S. I. PERLMUTTER[5], E. LEIN[2], N. C. DEMBROW[6], B. E. KALMBACH[2];
[1]Allen Brain Inst., Seattle, WA; [2]Human Cell Types, Allen Inst. For Brain Sci., Seattle, WA;

[3]Physiol. & Biophysics, [5]Dept Physiol. & Biophysics, Washington Natl. Primate Res. Ctr., [6]Physiol. and Biophysics, [4]Univ. of Washington, Seattle, WA

Abstract: *In vivo* neuronal activity is often coherent with specific frequency bands present in the local field potential. In macaque motor cortex, corticospinal neuron activity is coherent with prominent beta band oscillations (14-30 Hz) in local field potentials and EMG from contralateral muscles during motor planning and execution. This phenomenon is often assumed to rely on synaptic mechanisms, but intrinsic membrane properties are also likely to contribute. We tested the hypothesis that peri-threshold membrane oscillations and associated firing patterns vary across infragranlular pyramidal neuron types, and between neocortical regions by performing Patch-seq (combined single cell transcriptomics and patch clamp physiology) experiments in ex vivo macaque brain slices from motor (MCx) and temporal cortex (TCx). Patch-seq enabled us to group physiologically probed neurons into transcriptomically defined cell types for comparisons within and between regions based on single cell RNA-sequencing cell type taxonomies.

We found that spiking patterns during 10 s current injections varied significantly between infragranular cell subclasses and between areas. For the L5 extratelencephalic subclass (L5 ET), subthreshold oscillatory frequency during interspike periods differed between MCx and TCx. Membrane oscillations during interspike intervals in L5 ET neurons from both regions increased in power as a function of membrane depolarization (FFT strength; MCx: $r2 = 0.08$, $p < 0.001$, $n = 91$ observations from 59 neurons; TCx: $r2 = 0.04$, $p = 0.078$, $n = 82$ observations from 53 neurons). However, the peak frequency of these oscillations increased with membrane depolarization only in MCx L5 ET neurons when measured by autocorrelation (MCx: $r2 = 0.31$, $p < 0.001$, $n = 79$ observations from 52 neurons; TCx: $r2 = 0.002$, $p = 0.75$, $n = 66$ observations from 49 neurons) or Fourier analysis (MCx: $r2 = 0.32$, $p < 0.001$, $n = 91$ observations from 59 neurons; TCx: $r2 < 0.001$, $p = 0.146$, $n = 82$ observations from 53 neurons).

To test whether these oscillations were matched by similar firing rates, we quantified the coefficient of variation (CV) and modal firing rate during depolarizations. The CV of interspike intervals was more variable in MCx L5 ET neurons than TCx L5 ET neurons for firing rates up to 20 Hz, and the modal firing rate during spiking was well correlated with the subthreshold oscillation frequency in MCx L5 ET neurons but not TCx ($p < 0.001$, area effect, 2-way ANOVA). These findings highlight how regional and cell type specific intrinsic membrane properties might contribute to spike and network coherence in the primate neocortex.

Disclosures: S.D. Sawchuk: None. **C. Radaelli:** None. **X. Opitz-Araya:** None. **J.T. Ting:** None. **W.J. Spain:** None. **M. Hudson:** None. **S.I. Perlmutter:** None. **E. Lein:** None. **N.C. Dembrow:** None. **B.E. Kalmbach:** None.

Poster

PSTR002: Cellular Dynamics and Molecular Pathways in Brain Development and Regeneration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.27/A40

Topic: A.10. Development and Evolution

Support: 5UM1MH130981-02
1U01MH114812-01

Title: Morphoelectric properties of human excitatory transcriptomic types

Authors: *R. DALLEY[1], S. WALLING-BELL[1], A. MCCUTCHEON[1], J. A. MILLER[1], M. MALLORY[1], G. WILLIAMS[1], N. GORIOUNOVA[2], H. D. MANSVELDER[2], C. P. DE KOCK[2], G. TAMAS[3], J. T. TING[1], T. JARSKY[1], H. ZENG[1], E. LEIN[1], B. E. KALMBACH[1], S. A. SORENSEN[1], B. R. LEE[1];
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]Vrije Univ. Amsterdam, Amsterdam, Netherlands; [3]Univ. of Szeged, Szeged, Hungary

Abstract: Advances in transcriptomic studies of the human cortex have provided a framework to explore the diversity of brain cell types. As transcriptomic references gain recognition and cell type specific disease vulnerabilities are uncovered, elucidating the multimodal properties of the transcriptomic reference cell types becomes crucial for their interpretation. We expand on what is known about transcriptomic types (t-types) in human cortex, mapped to the Hodge et al. 2019, medial temporal gyrus reference taxonomy. The reference contains 24 excitatory types, 18 intratelencephalic (IT) types and 6 deep layer non-IT types. Using Patch-seq, a method to collect Morphology (M), Electrophysiology (E), and Transcriptomic (T) data from a single neuron, we investigated the morphoelectric and transcriptomic properties of human, excitatory neurons in cortical Layers 2-6 (L2-L6). Cortical excitatory neurons are typically known by their signature dendritic arbors, with a pronounced apical dendrite, which compartmentalizes and integrates synaptic input to compute and ultimately translate signals to downstream neurons. Our exploration delves into the ME properties of t-types and how the diversity of t-types may contribute to circuit dynamics. We find that ME properties generally align and separate by transcriptomic subclasses and t-types with a few notable exceptions, such as L6 IT, CT, and select L5 IT t-types. Within subclasses, neurons show functional distinctness, such as excitability, yet also exhibit variation as demonstrated by the width of the action potentials. Across t-types, we observe differences in apical tuftedness, reach, and presence, with much diversity existing in L6 IT types. We note two t-types, RORB CARM1P1 and RORB FILIP1L, that show ME and transcriptomic similarities to deep L3 t-types, as opposed to their original reference subclass assignment, L4 IT. The combined transcriptomic and morphoelectric properties of these neurons offer insights into how different neuron types may contribute to the flow of information across cortical circuits within the human cortex. Data are made publicly available at NeMO, DANDI and BIL.

Disclosures: R. Dalley: None. **S. Walling-Bell:** None. **A. McCutcheon:** None. **J.A. Miller:** None. **M. Mallory:** None. **G. Williams:** None. **N. Goriounova:** None. **H.D. Mansvelder:** None. **C.P. De Kock:** None. **G. Tamas:** None. **J.T. Ting:** None. **T. Jarsky:** None. **H. Zeng:** None. **E. Lein:** None. **B.E. Kalmbach:** None. **S.A. Sorensen:** None. **B.R. Lee:** None.

Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.01/A41

Topic: A.07. Developmental Disorders

Support: Simons Initiative for the Developing Brian, Award Number 1175658
SFARI Autism Rat Models Consortium grant 903332

Title: Hippocampal place cell activity in a rat model of GRIN2B-related neurodevelopmental disorder

Authors: *A. A. RÅSTEDT[1], A. J. DUSZKIEWICZ[2], P. C. KIND[1], P. A. DUDCHENKO[2], D. J. A. WYLLIE[1], E. R. WOOD[1];
[1]Ctr. for Discovery Brain Sci. & Simons Initiative for the Developing Brain, Univ. of Edinburgh, Edinburgh, United Kingdom; [2]Div. of Psychology, Univ. of Stirling, Stirling, United Kingdom

Abstract: In humans, heterozygous loss of function mutations in the *GRIN2B* gene are associated with neurodevelopmental disorders including autism and intellectual disability. The *GRIN2B* gene encodes GluN2B, a subunit of the *N*-methyl-D-aspartate (NMDA) receptor that plays a key role in neuronal development, learning, memory and synaptic plasticity. However, the effects of heterozygous loss of GluN2B on neuronal and circuit function are not well understood. In the hippocampus, NMDA receptor-mediated plasticity is required for long-term stability of the cognitive map represented by the activity of hippocampal place cells - pyramidal neurons which fire selectively in specific locations (place fields) of the environment. However, it is unclear to what extent *Grin2b* haploinsufficiency affects the activity or stability of hippocampal place cells. To address this, we used a *Grin2b*$^{+/-}$ rat model where GluN2B protein is expressed at 50% of the level seen in wild-type rats. Using silicon probes, we recorded neuronal activity in the hippocampal CA1 region while the rats shuttled for food on familiar and novel linear tracks, and quantified properties of place cells recorded in two sessions on the same track, spaced 6 hours apart. Our preliminary results suggest that while there is no difference in the spatial information (bits/spike) of the place cells between the genotypes, the place fields of *Grin2b*$^{+/-}$ rats are less stable between recording sessions on the novel track compared to place fields of wild-type littermates. Surprisingly, the place fields of the *Grin2b*$^{+/-}$ rats also seemed to be less stable than those of wild-types between two recording sessions on the familiar track. Together, these data suggest that *Grin2b* haploinsufficiency impairs NMDA receptor-dependent place field stability in rats. Further analyses will investigate whether these unstable cognitive maps are associated with impaired reactivation of neuronal ensembles during post-encoding sleep.

Disclosures: A.A. Råstedt: None. **A.J. Duszkiewicz:** None. **P.C. Kind:** None. **P.A. Dudchenko:** None. **D.J.A. Wyllie:** None. **E.R. Wood:** None.

Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.02/A42

Topic: A.07. Developmental Disorders

Support: Simons Initiative for the Developing Brain, Award Number 1175658

Title: Hippocampal synaptic plasticity and hippocampal-dependent memory in a rat model of GRIN2B-related neurodevelopmental disorder

Authors: *L. FRYER-PETRIDIS[1], A. VADHER[2], P. C. KIND[1], P. A. DUDCHENKO[2], D. J. A. WYLLIE[1], E. R. WOOD[1];
[1]Ctr. for Discovery Brain Sci. & Simons Initiative for the Developing Brain, Univ. of Edinburgh, Edinburgh, United Kingdom; [2]Div. of Psychology, Univ. of Stirling, Stirling, United Kingdom

Abstract: Heterozygous loss-of-function mutations in *GRIN2B*, which encodes the GluN2B subunit of the *N*-methyl-D-aspartate (NMDA) receptor, are associated with intellectual disability and autism spectrum disorder. The mechanistic links between *GRIN2B* haploinsufficiency and subsequent brain dysfunction are not well understood. Pharmacological and genetic manipulations of GluN2B-containing NMDA receptors have indicated a link between reduced functional expression of GluN2B and an impairment in the magnitude of NMDA receptor-dependent long-term depression (LTD) in the CA1 region of the hippocampus (Kutsuwada et al., Neuron 16:333-44, 1996 ; Liu et al., Science 304:1021-24, 2004). On the other hand, hippocampal NMDA receptor-dependent long-term potentiation (LTP) is less affected by loss of GluN2B function. We have investigated whether *Grin2b* haploinsufficiency affects these forms of plasticity in a rat model - the *Grin2b*$^{+/-}$ rat. Using conventional induction protocols (2 x 100 Hz for 1 s and 1 Hz for 15 minutes, for high- and low-frequency stimulation respectively), we found that the magnitude of LTP and LTD was unaltered in *Grin2b*$^{+/-}$ in comparison with WT slices at p12-14 and p28-35. In addition, we have assessed hippocampal NMDA receptor-dependent spatial memory. As NMDA receptors are required for the formation of long- but not short-term spatial memory, we predicted any deficits in *Grin2b*$^{+/-}$ rats would be restricted to long-term memory. We found that short- (1min) and long-term (24h) memory were preserved in the execution of a water maze reference memory task (Mixed sex cohort, WT: n=8, *Grin2b*$^{+/-}$: n=8). In the same cohort, *Grin2b*$^{+/-}$ rats showed no impairments in one-trial spatial memory at 20 min, 6 h and 24 h intervals in a delayed match-to-place water maze task. These findings indicate, perhaps surprisingly, that 50% loss of expression of GluN2B does not cause deficits in long-term spatial memory. Together, these findings suggest that heterozygous depletion of GluN2B is not sufficient to impair these forms of hippocampal plasticity and hippocampal long-term memory. As GluN2B expression is not restricted to the hippocampus, ongoing experiments are focussed on assessing forms of NMDAR-dependent memory reliant on different brain regions that may in turn contribute to the cognitive symptoms of *GRIN2B* haploinsufficiency in humans.

Disclosures: L. Fryer-Petridis: None. **A. Vadher:** None. **P.C. Kind:** None. **P.A. Dudchenko:** None. **D.J.A. Wyllie:** None. **E.R. Wood:** None.

Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.03/A43

Topic: H.03. Decision Making

Title: Interval timing in 16p11.2 deletion mice

Authors: M. MCMURRIN[1], A. OPPMAN[1], A. BOVA[1], M. A. WEBER[1], J. KIM[2], T. ABEL[3], *N. NARAYANAN[4];
[2]Departments of Neurosci. and Pharmacol., [3]Dept. of Neurosci. and Pharmacol., [1]Univ. of Iowa, Iowa City, IA; [4]Univ. of Iowa Roy J and Lucille A Carver Col. of Med., Iowa City, IA

Abstract: Copy number deletion of the 16p11.2 chromosomal region is present in approximately 0.6% of patients with autism spectrum disorder (ASD) and is associated with intellectual disability and cognitive impairments. However, the precise neurobiological mechanisms underlying cognitive symptoms in ASD are unknown. To address this, we investigated ASD-related cognitive deficits in a mouse model with a 16p11.2 deletion. This deletion is characterized by changes in both striatal physiology and dopamine D2 receptors. We studied cognitive function in these mice using an interval timing task that requires mice to estimate an interval of several seconds by making a motor response. Interval timing is relevant to study in ASD as it involves working memory for temporal rules, attention to the passage of time, requires striatal medium spiny neurons, and is impaired in individuals with ASD. We trained mice in an interval timing task where they are required to switch nosepokes after approximately 6 seconds. We found that 16p11.2 deletion mice performed better than littermate controls in this task, earning higher rates of reward. However, time perception in the 16p11.2 deletion mice may be altered, as evidenced by anticipatory response times, i.e., 16p11.2 deletion mice responded earlier compared to littermate controls. Previous work has demonstrated that sulpiride, a dopamine D2 receptor antagonist, reliably delays/prolongs interval timing, which we investigate in 16p11.2 deletion mice. Furthermore, we investigate the relationship between interval timing, spatial working memory performance, and motor performance. Altogether, these experiments will enhance our understanding of cognitive deficits associated with 16p11.2 deletion and related ASDs, and future experiments will investigate how changes in striatal physiology in 16p11.2 deletion mice correlate with interval timing behavior.

Disclosures: M. McMurrin: None. **A. Oppman:** None. **A. Bova:** None. **M.A. Weber:** None. **J. Kim:** None. **T. Abel:** None. **N. Narayanan:** None.

Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.04/A44

Topic: A.07. Developmental Disorders

Support: University of Iowa Hawkeye Intellectual and Developmental Disabilities Research Center (HAWK-IDDRC) P50 HD103556
NIH grant R01 MH 087463
NIH grant R01 DA 056113
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Title: A Chromosomal Region Linked to Neurodevelopmental Disorders Drives Repetitive Behaviors Through the Indirect Pathway Spiny Projection Neurons

Authors: *J. KIM[1], Y. VANROBAEYS[1], B. KELVINGTON[1], L.-C. LIN[1], S. L. FERRI[1], T. NICKL-JOCKSCHAT[2], T. ABEL[1];
[1]Univ. of Iowa, Iowa City, IA; [2]Otto von Guericke Univ., Magdeburg, Germany

Abstract: Repetitive behavior is a defining symptom observed across several neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), schizophrenia, and obsessive-compulsive disorder. The 16p11.2 hemideletion (16p11.2 del/+) is one of the most common genetic risk factors for NDDs, and carriers of 16p11.2 del/+ often exhibit cognitive and motor impairments, including repetitive behaviors. The striatum, the key neural substrate for motor control and habit formation, drives repetitive behaviors. However, the mechanisms underlying striatal dysfunction in repetitive behaviors are still not fully understood. In this study, we utilize rotarod training to study the emergence of repetitive behavior in 16p11.2 del/+ mice. These mice show enhanced motor learning on the rotarod and display significantly stereotyped paw kinetics, suggesting rotarod motor learning as a proxy for acquired stereotyped motor routines. Remarkably, fiber photometry recording of jGCaMP7f fluorescence in the dorsal striatum during rotarod training reveals distinct dynamics of striatal neuronal activity in 16p11.2 del/+ mice, indicating decreased calcium signaling on the first day of rotarod training but elevated calcium signaling on training day 4 compared to wt mice. Moreover, we observe that selective deletion of the 16p11.2 region in D2-spiny projection neurons (SPNs) induces enhanced motor learning, but not in D1-SPNs. Spatial transcriptomics analysis (Visium) indicates significant gene expression differences between the dorsal medial striatum and dorsal lateral striatum in 16p11.2 del/+ mice compared to wt mice, suggesting a subregion-specific role in motor learning. We also find D2-SPNs-specific 16p11.2 del/+ in the dorsal lateral striatum, but not in the dorsal medial striatum, affect motor learning on the rotarod, supporting a subregion-specific role in motor learning. Together, these results reveal that 16p11.2 del/+ causes the formation of repetitive behavior by impairing a specific striatal circuit activity and inducing region-specific gene expression changes in the striatum. These findings point D2-SPNs in the dorsal lateral striatum as potential therapeutic targets for ameliorating this symptom domain.

Disclosures: J. Kim: None. **Y. Vanrobaeys:** None. **B. Kelvington:** None. **L. Lin:** None. **S.L. Ferri:** None. **T. Nickl-Jockschat:** None. **T. Abel:** None.

Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

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Topic: A.07. Developmental Disorders

Support: The University of Iowa Hawkeye Intellectual and Developmental Disabilities Research Center (HAWK-IDDRC) P50 HD103556
NIH grant R01 MH087463
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Simons Foundation Autism Research Initiative (SFARI) grant 345034
NIH grant T32 GM067795
NIH grant F31 MH134542

Title: 16p11.2 hemideletion induces male-specific accumulation of dna damage in dopamine d1 receptor-expressing medium spiny neurons

Authors: *B. KELVINGTON[1], J. KIM[2], R. FAIR[1], J. KASUYA[1], T. ABEL[3];
[1]Univ. of Iowa, Iowa City, IA; [2]Departments of Neurosci. and Pharmacol., Univ. of Iowa, Iowa City, IA; [3]Dept. of Neurosci. and Pharmacol., Univ. of Iowa, Iowa City, IA

Abstract: Neurodevelopmental disorders (NDDs) encompass a wide range of challenging conditions with mostly unknown molecular etiologies and sex biases in prevalence and manifestation. 16p11.2 hemideletion (16p DEL) confers a high risk for NDDs with males more likely to have an NDD diagnosis and report greater impairments than females. Mice modeling 16p DEL exhibit sex-biased behavioral phenotypes relevant to NDDs, including a male-specific deficit in reward learning. However, the cellular and molecular mechanisms underpinning these sex-specific behaviors remain undefined. We found that dopamine receptor D1-expressing medium spiny neurons (D1+ MSNs), a major output neuronal population of the striatum, play a critical role in male-specific reward learning deficits mediated by 16p DEL. D1+ MSNs in the nucleus accumbens of 16p DEL males exhibit increased DNA double-strand breaks (DSBs), suggesting that disrupted DNA repair may underpin D1+ MSN dysfunction. Furthermore, the histone variant H2AX is hypoacetylated in 16p male D1+ MSNs, indicating diminished DSB repair capability. Female 16p DEL mice, on the other hand, exhibit higher levels of histone variants involved in DSB repair in D1+ MSNs following reward, highlighting a potential mechanism for female resilience in this model. These data implicate sex-specific alterations in DNA damage and repair as a molecular mediator of male bias in NDDs and pave the way for future therapeutic interventions to ameliorate the most challenging NDD symptoms.

Disclosures: B. Kelvington: None. **J. Kim:** None. **R. Fair:** None. **J. Kasuya:** None. **T. Abel:** None.

Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.06/A46

Topic: A.07. Developmental Disorders

Title: Characterization and Therapeutic Restoration of Sodium Channel Models for Autism Spectrum Disorders

Authors: *A. AL SANEH[1], L. GISSOT[1], M. HERMOSILLO ARRIETA[2], K. SCOTT[2], K. KRUTH[2], C. VAN DER HEIDE[2], A. J. WILLIAMS[2], C. AHERN[1];
[2]Neurosci., [1]Univ. of Iowa, Iowa City, IA

Abstract: The understanding of the mechanism behind Autism spectrum disorder (ASD) remains limited largely due to the disorder's remarkably complex etiology. Roughly five percent of ASD cases are monogenic in origin and can be traced to a single causal genetic variation. These examples provide an invaluable, simplified model of ASD that can be used to better correlate molecular dysfunction to phenotype. The highest monogenetic ASD risk gene is *Scn2a*, where premature termination variants (PTC) truncate the encoded protein, the sodium channel Nav1.2. Nonsense mutations leading to the abortive translation of the *Scn2a* gene result in reduced social interactions and repetitive behaviors as well as ataxia and cerebellar atrophy. Unfortunately, there are currently no *Scn2a* PTC mouse models available for autism research that would otherwise enable research avenues and therapeutic strategies. We have developed two *Scn2a* PTC mouse models (Tyr84X and Arg1626X), which are the first PTC autism rodent models to date. These mice are specific genetic models of ASD-linked *Scn2a* mutations that address specific differences in genotype-phenotype relationships. Given the broad context of their positions within the *Scn2a* gene, PTC mutations represent a significant challenge. To fill this gap, we have developed an approach using anticodon-edited transfer RNA (tRNA) to repair in-frame termination codons. This strategy is agnostic to the position of the variation and has the potential to be disease-modifying, by correcting of the primary defect of the disease, while sparing otherwise permanent germline modifications (i.e. base-editing or CRISPR). In this work, we show its therapeutic potential upon delivery into induced pluripotent stem cells (iPSCs) from patients with *Scn2a* PTC variants as well as *in vivo* mouse models. Using ribosomal profiling and mass spectrometry we have found that expressed suppressor tRNAs have minimal contact with native stop codons. In conclusion, the complexity of ASD and its genetic underpinnings, particularly the role of the Scn2a gene, necessitate innovative research approaches. The development of the first PTC autism rodent models, Tyr84X and Arg1626X, marks a significant step forward in this field. Moreover, the novel use of anticodon-edited transfer RNA (tRNA) to repair in-frame termination codons offers a promising therapeutic strategy. This approach, coupled with the demonstrated minimal interference of expressed suppressor tRNAs with native stop codons, pave the way for future research and potential treatments for many PTC-associated diseases, well beyond ASD.

Disclosures: A. al saneh: None. **L. Gissot:** None. **M. Hermosillo Arrieta:** None. **K. Scott:** None. **K. Kruth:** None. **C. van der Heide:** None. **A.J. Williams:** None. **C. Ahern:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); hC Biosciences.

Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

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Topic: A.07. Developmental Disorders

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Beijing Natural Science Foundation, grant number L222077
Beijing Natural Science Foundation, grant number IS23097

Title: Inhibition of proBDNF to Mature BDNF Conversion Induces ASD-Like Phenotypes in Vivo

Authors: *F. YANG[1], C. ZHU[2,3], M. KOJIMA[4,5], B. LU[6];
[1]Beijing Tiantan Hospital, Capital Med. Univ., Beijing, China; [2]GöTeborg Univ., GöTeborg, ; [3]Henan Key Lab. of Child Brain Injury and Henan Pediatric Clin. Res. Center, Inst. of Neurosci. and the Third Affiliated Hosp. of Zhengzhou Univ., Zhengzhou, China; [4]AIST, Biomed. Inst., Ikeda, Japan; [5]Biomed. Dept. of Applied Bioscience, Col. of Biosci. and Chem., Kanazawa Inst. of Technol. (KIT), Ishikawa, Japan; [6]Tsinghua Univ. Med. Sch., Beijing City.

Abstract: Autism Spectrum Disorders (ASD) comprise a range of early age-onset neurodevelopment disorders with genetic heterogeneity. Most ASD related genes are involved in synaptic function, which is regulated by mature brain-derived neurotrophic factor (mBDNF) and its precursor proBDNF in a diametrically opposite manner: proBDNF inhibits while mBDNF potentiates synapses. Here we generated a knock-in mouse line (BDNF$^{met/leu}$) in which the conversion of proBDNF to mBDNF is attenuated. Biochemical experiments revealed residual mBDNF but excessive proBDNF in the brain. Similar to other ASD mouse models, the BDNF$^{met/leu}$ mice showed reduced dendritic arborization, altered spines, and impaired synaptic transmission and plasticity in the hippocampus. They also exhibited ASD-like phenotypes, including stereotypical behaviors and deficits in social interaction. Moreover, the plasma proBDNF/mBDNF ratio was significantly increased in ASD patients compared to normal children in a case-control study. Thus, deficits in proBDNF to mBDNF conversion in the brain may contribute to ASD-like behaviors, and plasma proBDNF/mBDNF ratio may be a potential biomarker for ASD.

Disclosures: F. Yang: None. **M. Kojima:** None.

Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.08/A48

Topic: A.07. Developmental Disorders

Support: Simons Foundation Autism Research Initiative Grant (899599)
UCSF Physician Scientist Scholars Program
Brain and Behavior Research Foundation Grant (30821)

Title: Quantifying modulation of the startle response by capturing trial to trial variability

Authors: *E. A. MILLER[1], J. TON[2], N. YOKOTA[2], C. Y. LEE[2], G. D. HOLMES[3], D. B. KASTNER[2];
[1]Dept. of Psychiatry and Human Behavior, The Warren Alpert Med. Sch. of Brown Univ., Providence, RI; [2]Psychiatry and Behavioral Sci., Univ. of California, San Francisco, San Francisco, CA; [3]Neurosci. Dept., Wellesley Col., Wellesley, MA

Abstract: The acoustic startle response and its modulation by features such as a preceding sound, a “prepulse,” is measured to provide information about the internal state and processing of the brain. As such it has been proposed to be a relevant and translatable biomarker for psychiatric disease. However, the startle response is highly variable trial to trial. Traditionally, this trial-to-trial variability is managed by measuring some central tendency (e.g. mean or median) across multiple repeats of the same condition. Yet, the startle response for individual trials can be measured with high signal to noise, leaving open the possibility for a more accurate and reliable characterization of the startle response and its modulation. Here, we sought such an accurate characterization of the startle response by explicitly modeling the trial-to-trial variability. We applied principal component analysis (PCA) to the movement of animals in response to a sound, finding that the first principal component captures more than half of the variance in the movement of individual animals across trials. This PCA-based description of the startle response captures more variance in the response than traditional methods of using either the maximum or average response in a trial. We then used linear regression to model the variability in startle magnitude by regressing multiple covariates of the startle at the individual animal level. Those covariates included the loudness of the prepulse sound, the magnitude of the startle on the previous trial, the session number within a day, and the day of the session. The models were fit to a large amount of data from six, 1-hour long, sessions spread over three days for each rat. The resulting models explained a large fraction of the trial-to-trial variability across a broad range of startle sounds, and across a large cohort of rats. Capturing trial-to-trial variability was more accurate than traditional central tendency-based approaches, as assessed by cross validation. Thus, capturing trial-to-trial variability provides a better description of changes to the startle response under various conditions, providing multiple points of comparison to identify differences in startle due to genotype or other groupings of interest.

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Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

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Program #/Poster #: PSTR003.09/A49

Topic: A.07. Developmental Disorders

Support: DOD Grant AR220030
Hawk-IDDRC Grant P50 HD103556
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FamilieSCN2A Foundation Grant
Carver College of Medicine
Roy J. Carver Trust

Title: Unraveling SCN2A: exploring the effects of premature stop codons in mouse model behavior

Authors: *M. F. HERMOSILLO ARRIETA[1], K. SCOTT[2], A. AL SANEH[3], L. GISSOT[3], R. LI[1,4], K. BENSON[5], K. KRUTH[2], C. VAN DER HEIDE[1], G. F. BUCHANAN[4], C. AHERN[3], A. J. WILLIAMS[2];
[2]Psychiatry, [3]Mol. Physiol. and Biophysics, [4]Neurol., [5]Neural Circuits and Behavior Core, [1]Univ. of Iowa, Iowa City, IA

Abstract: The gene *SCN2A* encodes for the voltage-gated sodium channel, $Na_V1.2$, which plays a vital role in the propagation and backpropagation of action potentials. Premature termination codon (PTC) mutations in *SCN2A* have been linked to autism spectrum disorder and intellectual disability, which are associated with sociability and learning differences. PTCs are hypothesized to reduce protein by 50%, and are expected to cause similar behavioral phenotypes regardless of where they occur in the gene. Here, we have characterized the behavioral phenotypes of two *SCN2A* mouse models with patient PTC mutations, Y84X and R1626X. Preliminary data shows that *Scn2a*$^{Y84X/+}$ males have deficits in motor learning in the rotarod assay compared to their wild-type (WT) littermates despite normal locomotor function. This is not observed in the female *Scn2a*$^{Y84X/+}$ mice or in mice carrying the R1626X mutation. Additionally, female *Scn2a*$^{Y84X/+}$ mice show lower levels of anxiety-like behavior in the elevated zero maze compared to their WT counterparts. This trend has not been observed in male *Scn2a*$^{Y84X/+}$ mice or the R1626x line. Finally, we have not observed any impairments in either line associated with gait adaptation and associative learning on the Erasmus Ladder. These data suggest that behavioral phenotypes differ between these two mouse models of *SCN2A* PTCs. Future work will involve expanding our data set to be fully powered to detect sex differences and exploration of other behaviors, such as tail chasing and rearing, seizure activity, and sleep dysregulation. We aim to use these mouse models to understand the disease mechanisms of *SCN2A* PTCs.

Disclosures: **M.F. Hermosillo Arrieta:** None. **K. Scott:** None. **A. al saneh:** None. **L. Gissot:** None. **R. Li:** None. **K. Benson:** None. **K. Kruth:** None. **C. van der Heide:** None. **G.F. Buchanan:** None. **C. Ahern:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tevard Biosciences, hC Biosciences. **A.J. Williams:** None.

Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

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Topic: A.07. Developmental Disorders

Support: SFARI 4551
FamilieSCN2A Hodgkin Huxley Award
NSF Graduate Research Fellowship

Title: Scn2a haploinsufficiency induces neocortical hyperexcitability and spontaneous seizure-related activity in Long-Evans rats

Authors: ***S. E. TALOMA**[1], M. E. COULTER[2], R. NEVERS[1], R. P. D. ALEXANDER[1], B. SHARMA[3], G. WILLIAMS[1], C. HOLOBETZ[4], E. C. HAMADA[3], D. B. KASTNER[5], L. M. FRANK[6], K. J. BENDER[1];
[1]UCSF, San Francisco, CA; [2]Ctr. for Integrative Neurosci., Univ. of California San Fransisco, San Francisco, CA; [3]Univ. of California San Francisco, San Francisco, CA; [4]Sainsbury Wellcome Ctr., Sainsbury Wellcome Ctr., London, United Kingdom; [5]Psychiatry and Behavioral Sci., Univ. of California, San Francisco, San Francisco, CA; [6]Departments of Physiol. and Psyciatry, UC San Francisco, San Francisco, CA

Abstract: Genetic variation in *SCN2A* is a major risk factor for neurodevelopmental disorders, including developmental epilepsies, autism spectrum disorder (ASD), and intellectual disability. *SCN2A* encodes the voltage-gated sodium channel $Na_V1.2$, which, in mature neocortex, is expressed primarily in excitatory neuron dendrites. Loss-of-function (LoF) variants that suppress or eliminate $Na_V1.2$ function are associated with intellectual disability and ASD, and, in an estimated 20-30% of children, epilepsy with onset after the first 3 months of postnatal development. The mechanisms by which heterozygous loss of the $Na_V1.2$ in excitatory neurons leads to seizure remains poorly understood. Recently, Long-Evans rats heterozygous for the *Scn2a* gene have been developed as a new model for studying effects of $Na_V1.2$ loss. We find that these animals exhibit spontaneous seizure-like events as assayed by local field potential (LFP) recordings from the corpus callosum, with an increase in spike-wave discharges (SWDs) relative to wild type littermate controls. These SWDs occurred most frequently during periods of immobility. Consistent with cortical hyperexcitability *in vivo*, we observed increased excitability of pyramidal cells *ex vivo*. Whole-cell current clamp recordings from prefrontal layer 5 pyramidal cells showed that the rising phase of the action potentials (AP) was slower in *Scn2a*$^{+/-}$

rats, consistent with observations in *Scn2a*$^{+/-}$ mice. Despite this decrease in AP speed, overall AP frequency was increased for any given somatic current injection stimulus. This appears to be due to two mechanisms: first, the loss of $Na_V1.2$ in neocortical pyramidal cell dendrites leads to a lack of depolarization-dependent engagement of dendritic voltage-gated potassium channels. As such, neurons do not repolarize as effectively between APs, making them more primed for subsequent activity. Second, these neurons have increased input resistance, and further electrophysiological analysis suggests that potassium channel function in dendrites is reduced. Thus, direct interactions between $Na_V1.2$ and dendritic potassium channels, and long-term changes in dendritic potassium channel function due to heterozygous loss of $Na_V1.2$, may increase seizure burden in rat models. This suggests that these models may be useful for evaluating therapeutics for *Scn2a* loss-of-function related seizure.

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Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.11/A51

Topic: A.07. Developmental Disorders

Title: F1 generation SHANK3 heterozygous mutant Macaques exhibit stereotypy, cognitive and sensory deficits

Authors: *M. JIANG[1], X. YANG[2], R. LI[2], Z. REN[2], J. SHARMA[3], Z. YANG[4], F. A. AZEVEDO[3], W. MENEGAS[3], L. YANG[2], J. DAI[2], L. WANG[2], S. YANG[5], R. DESIMONE[6], G. FENG[3], Z. LU[2];
[1]MIT, cambridge, MA; [2]Shenzhen Inst. of Advanced Technol., Chinese Acad. of Sci., Shenzhen, China; [3]Brain and Cognitive Sci., MIT, Cambridge, MA; [4]Broad Inst., Chelsea, MA; [5]South China Agr. Univ., Guangzhou, China; [6]mcgovern Inst., MIT, Brookline, MA

Abstract: Phelan-McDermid syndrome (PMS) is a neurodevelopmental disorder with a terminal deletion in 22q13 that results in the loss of function of the SHANK3 gene. Loss of SHANK3 has been identified in gene-linkage studies to be strongly associated with ASD and intellectual disabilities. To gain further insights into SHANK3 mutation and associated behavioral, physiological and cognitive changes reflecting autism, we derived F1 generation mutants from our earlier developed founder SHANK3 macaques. Through a systematic phenotypic characterization, we found a consistent but heterogeneous distribution of behavioral signs that can be mapped onto human autism spectrum disorder. Auditory EEG/ ERP result suggest an early sensory processing deficit. We also found significant differences in some tests of learning

and cognition between mutants and controls. Resting state functional connectivity indicated a global hypoconnectivity but local hyper-connectivity, especially in visual sensory circuits. Our results from multiple tests suggest that the SHANK3 mutant phenotype in macaques can characterized in an unbiased manner.

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Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.12/A52

Topic: A.07. Developmental Disorders

Support: University of Michigan Protein Folding Disease Initative

Title: Dscam Deficiency Recapitulates Cognitive and Sensorimotor Phenotypes Observed in Autism Spectrum Disorder

Authors: *R. NEFF[1], K. STANGIS[2], G. G. MURPHY[3];
[1]Univ. of Michigan Molec & Behav Neurosci Inst. (MBNI), Ann Arbor, MI; [2]MBNI, Univ. of Michigan Molec & Behav Neurosci Inst. (MBNI), Ann Arbor, MI; [3]MNI/MIP, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: It is estimated that 1 in 36 children are affected by autism spectrum disorder (ASD) in the United States, which is nearly a twofold increase from a decade ago. As the name implies, ASD is characterized by a broad array of alterations in somatosensory, social, and cognitive domains. Recent research has put an emphasis on elucidating the genetic risk factors associated with ASD in hopes of better understanding the disorder and achieving a treatment. Through genome-wide association studies, the Down Syndrome cell adhesion molecule (*DSCAM*) has been identified as a significant risk factor for ASD, with many of the detected mutations conferring a *de novo* loss-of-function (dnLoF) that likely results in heterozygous individuals with diminished *DSCAM* expression. Previous studies in mouse models of *Dscam* deficiency have revealed perseverative behaviors and deficits in social interaction but have yet to fully explore the cognitive domains. Here, we conducted a comprehensive cognitive behavioral phenotyping which revealed that *Dscam*^{2J}+/- mice display a range of sensorimotor and cognitive impairments that are reminiscent of those observed in ASD. In the open field exploration task, we found that *Dscam* deficiency was sufficient to drive hyperactivity and heightened anxiety-like behaviors. This finding was accompanied by significant motor coordination deficits in the rotarod test. Spatial learning and memory were also seen to be impaired in the Morris water maze and Y-maze tasks. Furthermore, the *Dscam*^{2J}+/- mice exhibit substantial deficits in contextual fear learning that can be observed acutely (24hr-post) and extends far beyond the conditioning

sessions (30 days-post). Interestingly, implicit learning processes, namely procedural learning, remained intact. Our findings align with the behavioral spectrum commonly observed in childhood and adult ASD and support a reduction in *DSCAM* expression as a possible explanation of ASD-related behaviors. These results provide strong evidence for a disease model, i.e., *Dscam*^{2J}+/-, that could be useful for ASD research and therapeutic testing.

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Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

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Program #/Poster #: PSTR003.13/A53

Topic: A.07. Developmental Disorders

Support: R01 MH090740

Title: Distinct neuronal requirements for Islr2 in the formation of the internal capsule and cerebral peduncle - A central role for striatal direct pathway

Authors: *S. ALI[1,2], J. M. EHRMAN[3], P. MERCHAN SALA[4], R. R. WACLAW[5], K. J. CAMPBELL[6];
[1]Univ. of Cincinnati, Cincinnati, OH; [2]Developmental Biology, Cincinnati Children's Hospital and medical center, Cincinnati, OH; [3]Developmental Biol., Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [4]Developmental Biol., Cincinnati Children's Med. Ctr., Cincinnati, OH; [5]Exptl. Hematology and Cancer Biol., Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [6]Developmental Biol., Cincinnati Children's Hospl, Cincinnati, OH

Abstract: The internal capsule/cerebral peduncle is the major tract through which the axons of the descending (i.e., corticofugal and striatonigral) and ascending (i.e., thalamocortical) pathways travel through the brain. Disruptions in axon pathfinding through this tract have been associated with a spectrum of motor, cognitive, and emotional dysfunction. Thus, elucidating the cellular and molecular mechanisms involved in the formation of these axon trajectories is critical. Islr2 (Linx) is a transmembrane receptor that mediates critical axonal interactions involved in the formation of the internal capsule/cerebral peduncle. Previous work showed that loss of *Islr2* throughout the ventral forebrain, including striatal projection neurons, corridor cell and reticular thalamus, using *Dlx5/6-cre* abolishes internal capsule formation (Mandai et al. 2014 *Neuron*, **83**: 93). To distinguish the role of *Islr2* within these distinct neuronal populations to both internal capsule/cerebral peduncle and striatal circuit formation, we have utilized a combination of BAC transgenic reporter mice and immunohistochemical markers to trace striatonigral (*Sox8-GFP*), corticofugal (*Fezf2-tdTomato*), and thalamocortical (Netrin G1) axon trajectories throughout development in several different permutations of *Islr2* conditional mutant mice utilizing forebrain region-specific cre drivers. Firstly, we used *Isl1*^{cre}, which recombines in both the direct pathway striatal projection neurons (dSPNs) and corridor cells to recombine *Islr2*

and found this resulted in a complete loss of the internal capsule/cerebral peduncle including dSPN, corticofugal and surprisingly thalamocortical axons. Despite the severe dSPN axon defects in these conditional mice, the corridor appears to have formed correctly implicating a role for Islr2 directly in the dSPNs themselves. In order to distinguish a role for *Islr2* specifically in SPNs versus corridor cells we used *GPR88-cre* to recombine *Islr2* in maturing SPNs. This resulted in defasciculation of dSPN and corticofugal axons while thalamocortical axons were relatively intact. Finally, to examine a role for *Islr2* in the reticular thalamus, which serves as a guiderail for descending and ascending fibers in the internal capsule, we used $Foxd1^{cre}$ to inactivate *Islr2* in the prethalamus/reticular thalamus. These *Islr2* conditional mutants showed no overt defects in dSPN, corticofugal or thalamocortical axons within the internal capsule/cerebral peduncle. Taken together, our results highlight the central role that *Islr2* on dSPN axons plays in the correct assembly of the internal capsule/cerebral peduncle within the developing mammalian forebrain.

Disclosures: S. Ali: None. **J.M. Ehrman:** None. **P. Merchan Sala:** None. **R.R. Waclaw:** None. **K.J. Campbell:** None.

Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.14/A54

Topic: A.07. Developmental Disorders

Support: NIH Grant R15S088776

Title: Early-life communication differences among ns-pten mice

Authors: *T. R. BRADISH[1], G. CHELLIAH[2], K. BLANDIN[3], D. A. NARVAIZ[3], J. J. THAYIL[2], J. N. LUGO, Jr.[3], C. LAU[3];
[1]Psychology and Behavioral Neurosci., Baylor Univ., Waco, TX; [2]Baylor Univ., Waco, TX; [3]Psychology and Neurosci., Baylor Univ., Waco, TX

Abstract: Background Autism spectrum disorder (ASD) is a developmental, neurological disorder that is estimated to affect 1 in 36 children. According to the DSM-V, ASD is characterized by social communication and interaction deficits, as well as restricted, repetitive behavioral patterns. The mechanistic target of rapamycin (mTOR) pathway is associated with regulating cell growth and migration in cellular resources. It has been uncovered that a deletion or mutation of the phosphate and tensin homolog (PTEN) on chromosome ten is a suppressor of the mTOR pathway. Loss in function that is mitigated by a PTEN deletion has been associated with ASD. In fact, 25% of individuals with a PTEN mutation meet ASD criteria or have characteristics of it. In the present study, we aimed to characterize the communication found in the neuronal subset-specific deletion of PTEN across critical points of early development. Methods We used a neuronal subset-specific PTEN (NS-PTEN) mouse model to investigate the

communication differences among wildtype, heterozygous, and knockout genotypes (n=12 per genotype). Ultrasonic vocalizations (USVs) were used to examine these differences, as they have shown to be an adequate tool to assess communication in mice. Mouse pups generally vocalize during their first 2 weeks of life and are emitted to elicit a retrieval response from the dam. In our model, we separated the pups from the dam and individually isolated them for 2 minutes in a chamber that recorded their calls. We chose postnatal days (PD) 10 and 12 to evaluate critical time point differences. GraphPad Prism 7 software and SPSS 21.0 were used to analyze the data. We evaluated differences of genotype on call types and aspects of total calls. Results Initial data analyses for PD10 male pups, found no statistically significant differences in the quantity of vocalizations produced between genotypes, nor were there significant variances in the spectral properties of the emitted USVs (i.e., call duration, latency to first call, amplitude, and pitch). The distribution of call types was only statistically significant in the flat calls between the heterozygous and knockout mice ($\bar{D} = -4.583$, $p < .05$). Discussion We expect to find changes in the quantitative characteristics of the ultrasonic vocalizations between the wildtype, heterozygous, and PTEN knockouts, with the PTEN knockout having a more severe change to the quantitative characteristics in comparison to the heterozygous and wildtype mice between age groups. Analyses for PD12 will also be presented. We believe that our results will be able to give us a more comprehensive view of the developmental profile of USVs in NS-PTEN mouse pups among genotypes.

Disclosures: **T.R. Bradish:** None. **G. Chelliah:** None. **K. Blandin:** None. **D.A. Narvaiz:** None. **J.J. Thayil:** None. **J.N. Lugo:** None. **C. Lau:** None.

Poster

PSTR003: Circuit and Behavioral Alterations in Animal Models for Autism

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.15/A55

Topic: A.07. Developmental Disorders

Support: MEXT/JSPS KAKENHI Grant Number JP21K20705
Shinkei Kenkyujo
Meiji Yasuda Kokoro no Kenkou Zaidan
Boshi Kenko Kyokai

Title: Transient inhibition of developing Purkinje cells causes male-specific social and fine motor deficits "vulnerable male cerebellum hypothesis"

Authors: *S. KAMIJO[1], H. MIWA[2];
[1]Natl. Ctr. of Neurol. and Psychiatry, Kodaira, Tokyo, Japan; [2]Natl. Ctr. of Neurol. and Psychiatry, Natl. Inst. of Mental Hlth., Tokyo, Japan

Abstract: Autism spectrum disorder (ASD) is four times more common in boys. While genetic factors play a significant role in ASD pathogenesis, the cause of the biased sex ratio remains

unclear. Previous studies have shown that cerebellar Purkinje cells are involved in the development of ASD. However, most studies used genetic mouse models with irreversible cerebellar impairment, and the tested subjects were primarily male.
To examine the critical period of each ASD-like phenotype, we used model mice expressing inhibitory DREADD specifically in cerebellar Purkinje cells, and their activity was transiently suppressed by oral administration of clozapine N-oxide (CNO) from postnatal day 11-15 (short inhibition) or postnatal day 11-20 (long inhibition). Both male and female mice are subjected to behavioral analysis to assess the sex difference.
Although there was no significant difference in gross cerebellar histology, male-specific social deficit was observed in a three-chamber test. We also found male-specific fine motor dyscoordination in a rotarod test. These male-specific phenotypes were consistent for both short and long-inhibition cohorts. However, acoustic sensory processing was differently affected in males and females. Repetitive self-grooming behavior was unaffected. To analyze the responsiveness of gene expression profile against aberrant cerebellar activity, we performed RNA-seq of the cerebellum and cortex with or without Purkinje cell inhibition using both sexes. Our findings suggest that transient dysfunction of developing Purkinje cells can lead to male-specific social and fine motor deficits. Interestingly, ASD patients often exhibit awkwardness, a trait more commonly observed in males. We propose that the vulnerability of the developing male cerebellum is a shared underlying cause of the two conditions which could potentially explain their male-biased prevalence.

Disclosures: **S. Kamijo:** None. **H. Miwa:** None.

Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.01/A56

Topic: A.09. Adolescent Development

Support: R01MH110438 (PI: Vasudevan)
S10MH133643 (PI: Vasudevan)

Title: Endothelial $GABA_A$receptor signaling modulates postnatal brain development

Authors: *K. HOSSAIN, S. ELBAKRI, J. LIN, E. ABAD, A. VASUDEVAN;
Huntington Med. Res. Inst. (HMRI), Pasadena, CA

Abstract: Endothelial $GABA_A$ Receptor Signaling Modulates Postnatal Brain Development
Kazi Helal Hossain, Said Elbakri, Justin Lin, Emily Abad, and Anju Vasudevan
Angiogenesis and Brain Development Laboratory, Department of Neurosciences, Huntington Medical Research Institutes (HMRI), 686 S Fair Oaks Avenue, Pasadena, CA, 91105, USA.
Abstract: The central nervous system (CNS) acquires its vasculature by angiogenesis, a process that is critical for its development and repair. Our findings have offered new perspectives on

intrinsic regulation of angiogenesis and highlighted the importance of vascular diversity during brain development. Pre-formed vascular networks act as a blueprint for the formation of the neocortex. They are strategically positioned, spatially and temporally to provide support and critical guidance cues to instruct key events of brain development. Recently, our studies uncovered a novel GABA signaling pathway in embryonic forebrain endothelial cells that works independently from neuronal GABA signaling. It revealed that disruptions in endothelial GABA signaling from early embryonic stages can directly contribute to the origin of psychiatric disorders including autism, epilepsy, schizophrenia, anxiety, and depression. The vascular GABA signaling pathway persists into the postnatal phase, exhibiting distinct characteristics compared to its embryonic counterpart. Here we demonstrate the fundamental mechanisms of action of endothelial $GABA_A$ receptors during the postnatal period with new significance for neocortical development and disease. We show novel roles for endothelial $GABA_A$ receptor signaling in vascular regression and stabilization that is indispensable for postnatal brain development and can differentially shape blood flow and adult behavioral paradigms. Our results unveil a previously unexplored dimension of neurovascular interactions, offering fresh insights into the cellular and molecular landscape governing the development of the neocortex. Importantly, these findings carry profound implications for our understanding of neuropsychiatric disorders, opening new avenues for therapeutic interventions and diagnostic strategies.
Disclosures: None
Support: R01MH110438 and S10MH133643 (PI: Vasudevan)

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Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.02/A57

Topic: A.09. Adolescent Development

Support: This study was funded through a Tobacco Related Disease Research Program project grant (22RT-0103A, S.L.)

Title: Hypersensitivity of The Nicotinic Acetylcholine Receptor Subunit CHRNA2 L9'S/L9'S In Female Adolescent Mice Mediates Sexually Dimorphic Nicotine-Induced Facilitation of Hippocampal-Dependent Learning and Memory

Authors: *A. WELLS[1], C. MOJICA[2], S. LOTFIPOUR[3];
[1]Univ. of California Irvine, Irvine, CA; [2]Pharmacol., UC Irvine, Irvine, CA; [3]Emergency Med., Pharmacol., & Pathology, Univ. of California, Irvine, Irvine, CA

Abstract: The nicotinic acetylcholine receptor (nAChR) has been shown to play a functionally distinct role in the development of the adolescent brain through the modulation of neurotransmitter release across various neurodevelopmental milestones. *CHRNA2* encodes for the *CHRNA2*$^{L9'S/L9'S}$ nicotinic acetylcholine receptor associated with CA1 oriens lacunosum moleculare GABAergic interneurons and is associated with learning and memory. Prior literature consistently supports the finding that chronic nicotine exposure during adolescence leads to an impairment in learning in adulthood. Previously, we found that adolescent male hypersensitive *CHRNA2*$^{L9'S/L9'S}$ mice had impairments in learning and memory during a pre-exposure-dependent contextual fear conditioning task that could be rescued by low-dose nicotine exposure. In this study, female adolescent *CHRNA2*$^{L9'S/L9'S}$ mice and wild-type (WT) littermate controls were exposed to saline or nicotine (0.09 mg/kg) using a hippocampus-dependent task of pre-exposure-dependent contextual fear conditioning (Figure 1). Alterations in freezing behavior—an indication of learning—were compared between *CHRNA2*$^{L9'S/L9'S}$ and WT female adolescent mice as well as against adolescent male *CHRNA2*$^{L9'S/L9'S}$ and WT mice. We found that nicotine-treated adolescent WT female mice had significantly greater freezing behavior than both saline-treated WT mice and nicotine-treated *CHRNA2*$^{L9'S/L9'S}$ female mice. Nicotine-treated adolescent *CHRNA2*$^{L9'S/L9'S}$ female mice did not have enhanced freezing behavior on context test (CT) day when compared with saline-treated *CHRNA2*$^{L9'S/L9'S}$ female mice. These results indicate that hypersensitivity of the *CHRNA*2 gene in female adolescent mice produces deficits in nicotine-dependent learning and memory in the hippocampus. These results are contrasted with the results obtained in the previously published male data where we found that male hypersensitive *CHRNA2*$^{L9'S/L9'S}$ mice had impairments in learning and memory that could be rescued by low-dose nicotine exposure. Thus, nicotine exposure mediates a sexually dimorphic pattern of learning and memory in WT and *CHRNA2*$^{L9'S/L9'S}$ adolescent mice exposed to a pre-exposure-dependent contextual fear conditioning paradigm. At present, the mechanism driving sexual dimorphisms between nicotine-exposed adolescent *CHRNA2*$^{L9'S/L9'S}$ mice is unknown. Further research must be conducted in both *in-vitro* and *in-vivo* studies examining the role of -expressing nAChR signaling mediating sex-dependent effects.

Disclosures: A. Wells: None. **C. Mojica:** None. **S. Lotfipour:** None.

Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.03/A58

Topic: A.09. Adolescent Development

Support: R01AA209403
R21AA028088
P50AA017823
F31AA0304550
T32GM108563
F32AA031396

Title: Binge-like alcohol consumption throughout adolescence disrupts prelimbic somatostatin signaling

Authors: *L. SEEMILLER[1], A. SICHER[2], K. GRIFFITH[1], D. BROCKWAY[3], M. HOSSAIN[4], P. J. DREW[3], N. A. CROWLEY[5];
[1]Penn State Univ., University Park, PA; [2]Penn State Univ. Neurosci. Program, University Park, PA; [3]Pennsylvania State Univ., University Park, PA; [4]Biomed. Engin., Pennsylvania State Univ., State College, PA; [5]Dept. of Biol., Penn State Univ., University Park, PA

Abstract: Alcohol exposure disrupts normal functioning of inhibitory GABAergic neurons, including SST neurons, particularly within cortical regions. These changes are likely to be involved in the heightened risk of psychiatric disorders seen with chronic alcohol use. Here, we examined SST cell and peptide functioning and related behavioral outcomes after adolescent binge-like drinking. Male and female C57BL/6J and SST-Cre:Ai32 mice (n=10/sex/treatment) consumed alcohol or water in a drinking-in-the-dark (DID) paradigm throughout adolescence (PND 29-54) and were tested for SST or behavior changes 30 days after cessation of DID. Generalized linear modeling was used to examine the influence of sex, total alcohol consumed, and last alcohol binge on dependent measures while accounting for cohort and litter effects. 30 days after cessation of DID, sex significantly interacted with total alcohol consumed throughout adolescence, where latency to enter an open arm was decreased in males and increased in females in alcohol-exposed groups. A similar effect of sex and adolescent alcohol was also observed for the number of entries into an open arm, which again was increased in males and decreased in females due to adolescent alcohol exposure. Taken together, this suggests that males may be more susceptible to increases, while females may experience reductions in exploratory behaviors 30 days after drinking. Behavioral changes correspond to biological data showing prelimbic SST dysfunction after adolescent alcohol exposure. These findings suggest that adolescent alcohol exposure causes persistent sex-specific changes in exploratory behavior, likely via disruption of prelimbic SST signaling. Future work will characterize changes in prelimbic SST release after adolescent alcohol and explore SST as a therapeutic target for treatment of alcohol-induced damage.

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Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.04/A59

Topic: A.09. Adolescent Development

Support: NSERC RGPIN-2020-06929
NSERC PGS D
CFI 30215

CRC 2018-00023
Alberta Innovates
Chinook Summer Research Award

Title: Early life adversity in rats leads to social, cognitive, and neural deficits

Authors: *J. R. HAM[1], V. RICHMOND[1], E. CANTWELL[1], B. HASTIE[2], H. SLOBODIAN[1], N. HONG[1], A. N. IWANIUK[1], S. M. PELLIS[1], R. J. MCDONALD[1];
[1]Univ. of Lethbridge, Lethbridge, AB, Canada; [2]Univ. of Lethbridge, Lehtbidge, AB, Canada

Abstract: Mood disorders, such as depression and anxiety, affect millions of people, young and adults alike, with anxiety being the most common psychiatric disorder. Despite anxiety being the most common childhood and adolescent psychiatric disorder, few animal models investigate mood disorders in immature individuals. Many pre-clinical rodent models of mood disorders exist, including exposing animals to chronic stress during early development. Here, we used an early life adversity (ELA) model to induce mood disorders in rats. To do so, we separated Long Evans pups from their siblings and mother, daily, for 3 h from postnatal day 3 to 14. We tested 16 females and 20 males that underwent ELA against 17 female and 17 male control rats. To assess sociality, we evaluated play behavior in both groups and pairs of rats when they were juveniles and adults. During adulthood, we also used the Morris water task, discriminative fear conditioning to context, conditioned place preference, and elevated plus maze to assess the effects of ELA on adult cognition. Following behavioral testing, the brains were Golgi stained to examine neurons in medial prefrontal cortex (mPFC), an area involved in both social and non-social cognitive domains. When compared to controls, ELA rats, of both sexes, exhibited social anxiety, playing less with unfamiliar animals, but normally with cage mates. When the rats played in groups and given a choice between an ELA or control partner, ELA rats preferred to play with ELA partners, while controls showed no preference between partners. In adulthood, both female and male ELA rats engaged in low quality play (i.e., less turn taking and less symmetry in play relationships) and many pairs escalated playful interactions to aggression compared to control animals. As adults, ELA females showed memory deficits in the cue-place version of the water task, impaired conditioned preference, and spent more time in the open arms in the elevated plus maze. Preliminary results from the mPFC, where pyramidal cells from Layer III were traced using virtual microscopy, suggests that both ELA male and female rats have fewer branches in both the apical and basilar dendrites. These results suggest that ELA induces social anxiety and neural deficits in both sexes, with females having additional non-social cognitive deficits and altered fear regulation.

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Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.05/A60

Topic: A.09. Adolescent Development

Support: Whitehall Foundation

Title: Adolescent maturation of neural circuits underlying social functions in mice

Authors: S. VARMAN, A. SMITH, A. KALATHIL, ***L. COUTELLIER**;
Ohio State Univ., Columbus, OH

Abstract: The transition from childhood to adulthood is marked by maturation of social behaviors to allow an organism to gain independence from parental care and to respond to the demands of an adult social life. For instance, while social interactions are highly rewarding during adolescence, they become less rewarding in adulthood when "cautious" investigative behaviors become predominant. Recent advances in the study of the adolescent brain have attempted to link developmental changes within neural circuits and maturation of social behaviors; unfortunately, a complete understanding of the mechanisms governing reorganization of neural circuits and their contribution to behavioral maturation is lacking. Here, we provide an in-depth analysis of qualitative and quantitative changes in social behaviors and social motivation in male and female mice from early adolescence (postnatal day PD28), to mid-adolescence (PD35 and PD45), until adulthood (PD80) to link them to developmental changes in activity of fronto-striatal (reward) circuit using tracers and immunohistochemistry approaches. We noticed that males display more cautious social interactions as early as PD35 with less direct approaches and nose-nose sniffing, and more following behaviors compared to PD28 mice. This is paralleled by reduced social motivation as early as PD35. These behavioral changes are associated with decreased expression of cFos in prefrontal neurons projecting to the ventral striatum from PD28 to PD80, neurons that are also surrounded by an increased number of parvalbumin buttons. In females, we observed similar changes at the neuronal level and in social motivation. However, the maturation of social behaviors during a social interaction appears later in females than in males (PD45 vs PD35) and is marked by a decrease in following and sniffing behaviors. Altogether, our findings provide an exhaustive description of changes in social behaviors during the transition from childhood to adulthood in mice, demonstrating that social behavioral patterns follow a sex-specific trajectory in term of timing and type of social behaviors. However, the underlying neural mechanisms seem to be similar in males and females, with increased inhibitory inputs onto prefrontal neurons regulating reward processes, likely reducing the rewarding nature of social interaction with age. Further investigations will determine if the decreased activity of fronto-striatal (reward) circuits are paralleled by increased activity of fronto-amygdala (threat assessment) circuits.

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Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.06/A61

Topic: A.09. Adolescent Development

Support: R21MH121836
R01MH131053

Title: Synaptic Adhesion Molecule IgSF9b Regulates Inhibitory Synaptic Maturation During Prefrontal Adolescent Development

Authors: *J. CLARIN, C. ALEXANDROPOULOS, A. KEITH, S. YANG, N. MACK, Y. LI, W.-J. GAO;
Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: An individual neuron typically receives both excitatory and inhibitory synaptic inputs, resulting in a precise configuration of opposing signals that govern overall firing activity. This phenomenon gives rise to fine-tuned gating of neural activity and is directly relevant to psychiatric disorders such as schizophrenia, autism spectrum disorders, and epilepsy that are typified by pathological tips of the excitatory/inhibitory (E/I) scales. While many genes have been linked to disease-causing alterations in excitatory synaptic function, far fewer have been implicated specifically in inhibitory synaptic dysregulation. This is due in part to the general lack of knowledge of the complement of organizing proteins that show specificity to inhibitory synapses, and thus presents a profound knowledge gap in our understanding of how these synapses form, develop, and decay. Critically, prefrontal inhibitory synapse maturation is markedly upregulated during adolescence, coinciding with the developmental stage during which psychiatric conditions typically emerge. To obtain a better grasp of how inhibitory synaptic adhesion molecules influence E/I balance and prefrontal inhibitory circuit development relevant to psychiatric disorders, we are exploring the function of the inhibitory synapse-specific cell adhesion molecule, IgSF9b, that has been linked to both major depression and schizophrenia. Our findings suggest that IgSF9b plays a pertinent role at inhibitory synapses targeted to prefrontal pyramidal cells, which canonically project to other brain regions to exert top-down control of behavior. Specifically, adolescent genetic knockdown of IgSF9b leads to deficits in cognitive and affective behaviors, in a sex-dependent manner. Physiologically, knockdown decreased the frequency of inhibitory synaptic currents in young adulthood and altered pyramidal cell excitability. Our findings suggest that disruption of adhesion processes during synaptic critical periods can have outsized effects on prefrontal circuitry and behaviors in adulthood.

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Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.07/A62

Topic: A.09. Adolescent Development

Title: Establishing cellular identities of the medial pulvinar and their role in developing thalamocortical connections

Authors: *A. FAN[1,2], J. KLEVE[1], A. ROMANOWSKI[1], J. SCOTT[1], G. J. FISHELL[3], J. A. BOURNE[1];
[1]Section on Cell. and Cognitive Neurodevelopment, Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Monash Univ., Melbourne, Australia; [3]Harvard Med. Sch., Jamaica Plain, MA

Abstract: A hallmark of several neurodevelopmental disorders is an excitation-inhibition imbalance in prefrontal cortex (PFC) attributed to dysfunction of cortical interneurons, especially parvalbumin (PV) cells. In primates including humans, the thalamus exerts direct modulatory control of this circuit through two major nuclei: the medial pulvinar (PM) and the mediodorsal nucleus (MD). However, the relative contributions of these two nuclei on cortical PV cells, particularly across postnatal development, remain unknown. Here, we investigated thalamic development in common marmoset monkeys (*Callithrix jacchus)* across key timepoints: infancy (PD0-3), juvenile (PM3-5), adolescence (PM8-10), and adulthood (>1.5y) (total n = 8, both sexes) using a comprehensive approach incorporating immunohistochemistry (IHC) and in situ hybridization (ISH). We show distinct expression patterns of glutamate and GABA receptor subunits in the two thalamic nuclei, dynamically evolving across developmental stages. Next, we piloted the use of a PV-specific S5E2 enhancer in the developing marmoset for the first time (adult n = 3, infant n = 1), for the specific execution of monosynaptic tracing using pseudotyped rabies. Remarkably, all cortical projections from the PM onto inhibitory PV cells were found to be excitatory and stained positive for calbindin, suggesting that the thalamus acts as a driver for cortical inhibition, modulated by local interneuron circuits. Interestingly, we have identified the presence of RNA transcripts for DRD2, a schizophrenia risk gene, in the cortex-projecting cells within the PM, despite a significant lack of corresponding protein expression, raising questions about the trafficking and localization of the receptor and role of dopamine in thalamocortical circuits. We use anterograde tracing from the PM to investigate the expression of synaptic receptors on these cell terminals. These findings contribute to our understanding of thalamocortical circuits, highlighting the unique features of the medial pulvinar and its role in neurodevelopmental processes in the primates, including humans.

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Poster

PSTR004: Adolescent Development: Animal Models

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.08/A63

Topic: A.09. Adolescent Development

Support: CIHR (PJT 399790)
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Natural Sciences and Engineering Research Council of Canada (RGPIN-2017-06344)

Title: Age- and sex-dependent recruitment of the prefrontal-amygdala pathway in fear extinction

Authors: *J. WILKIN, M. ARRUDA-CARVALHO;
Psychology, Univ. of Toronto Scarborough, Toronto, ON, Canada

Abstract: Fear conditioning is a valuable tool in assessing emotional memory in animal models, resulting in an adaptive fear response that is critical for survival. Fear learning and extinction are developmentally regulated in humans and rodents. Specifically, rodents show two behavioral phenotypes of extinction: juveniles exhibit a permanent extinction that does not result in spontaneous recovery of the fear response (immature-type extinction), whereas in adults fear responses tend to re-emerge spontaneously following extinction training. The switch between immature- and adult-type extinction occurs around the juvenile stage in mice, and coincides with developmental changes in prefrontal-amygdala synaptic connectivity. While prefrontal cortex projections to the basolateral amygdala (BLA) play a well-established role in extinction learning, the precise timing and contribution of the prefrontal-BLA circuit to the extinction switch remains unknown. Here, we investigated the necessity of the infralimbic (IL) - BLA pathway in extinction during early life using optogenetics. Mice were trained to associate a tone with a foot-shock, followed by extinction training and spontaneous recovery a week later. Females, but not males, exhibited immature (persistent) extinction at P21, which switched to adult-type extinction by P25. Optogenetic inhibition of the IL-BLA pathway during extinction learning suppressed extinction retrieval in males but not P21 females, suggesting that IL-BLA recruitment drives the developmental onset of adult-type extinction.

Disclosures: J. Wilkin: None. **M. Arruda-Carvalho:** None.

Poster

PSTR004: Adolescent Development: Animal Models

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Program #/Poster #: PSTR004.09/A64

Topic: A.09. Adolescent Development

Support: ARC grant DP220103309

Title: The influence of basolateral amygdala projections on the development of parvalbumin interneurons in the rat prefrontal cortex across adolescence

Authors: *E. COHEN[1], K. D. BAKER[2], K. ZIMMERMANN[1], R. RICHARDSON[1]; [1]Psychology, The Univ. of New South Wales, Sydney, Australia; [2]Psychology, Counselling and Therapy, La Trobe Univ., Melbourne, Australia

Abstract: The brain's fear network undergoes protracted and asynchronous development, with basolateral amygdala (BLA) projections to the prefrontal cortex (PFC) forming before reciprocal projections. Although neuronal development in these regions starts in infancy, fibre proliferation and synaptic connections continue to mature throughout juvenility and adolescence, finally stabilising in adulthood. The PFC is a late-maturing structure which receives increasing input from the BLA throughout development. Here, we tested the hypothesis that neuronal input from the BLA early in life drives the development of the PFC. BLA fibres to the PFC synapse on pyramidal neurons and parvalbumin (PV)-expressing interneurons. These inhibitory interneurons modulate the activity of the PFC and are required for some aspects of fear-related learning. Although the number of PV-expressing cells in the PFC is stable across age, PV protein levels increase from juvenility to adulthood, indicating continued development of existing interneurons. One marker of neuronal development is the formation of perineuronal nets (PNNs), which are extracellular structures that stabilise synapses. The appearance of PNNs represents the closure of critical windows of plasticity. Previous work from our lab has shown that PNNs surrounding PV interneurons undergo substantial proliferation in the PFC during early adolescence. To test the hypothesis that BLA afferents are required for PFC development, rats were given unilateral excitotoxic lesions of the BLA as juveniles (at P22), and were then euthanised in early adolescence (P35), late adolescence (P50), or adulthood (P70). Analysis of deep and superficial layers of the prelimbic and infralimbic subdivisions of the PFC was performed with immunohistochemistry. PV neuron development was assessed with fibre quantification, cell counts, and colocalisation with surrounding PNNs. Lesioned and non-lesioned hemispheres were compared within each animal in the three age groups. This work aimed to provide mechanistic insight into the development of fear-related structures in the PFC.

Disclosures: E. Cohen: None. **K.D. Baker:** None. **K. Zimmermann:** None. **R. Richardson:** None.

Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.10/A65

Topic: A.09. Adolescent Development

Support: NIH Grant R01-MH086507
NIH Grant R01-MH127850

Title: Early life adversity arrests the normal gain of prefrontal GABA function during adolescence

Authors: *E. ARTUR DE LA VILLARMOIS, E. FLORES-BARRERA, K.-Y. TSENG;
Univ. of Illinois Chicago, Chicago, IL

Abstract: Early life adversity (ELA) has been known to impact the development and maturation of corticolimbic connectivity including the prefrontal cortex (PFC). It is therefore conceivable that early life events contribute to shaping the developmental trajectory of PFC maturation during adolescence. To test this idea, we implemented a maternal separation paradigm and assessed whether the adolescent trajectory of GABAergic transmission in the PFC is differentially compromised by the developmental window of ELA exposure (P2-10 vs. P11-20). We found that PFC pyramidal neurons recorded from animals exposed to ELA from P2 to P10 exhibit a normal developmental gain of inhibitory postsynaptic current (IPSC) frequency. Interestingly, such gain of GABA function was not observed following ELA exposure from P11 to P20. This GABAergic impairment is accompanied by a lower frequency of excitatory postsynaptic current (EPSC) onto local fast-spiking and non-fast-spiking interneurons. Collectively, our findings indicate that PFC inhibitory synapses are preferentially susceptible to ELA from P11 to P20, likely through disruption in the recruitment of local fast-spiking and non-fast spiking interneurons during adolescence.

Disclosures: E. Artur De La Villarmois: None. **E. Flores-Barrera:** None. **K. Tseng:** None.

Poster

PSTR004: Adolescent Development: Animal Models

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.11/A66

Topic: A.09. Adolescent Development

Support: Research grant from the Whitehall Foundation to LC

Title: Role of prefrontal parvalbumin cells on the development of social behaviors during adolescence

Authors: *K. LIN[1], L. COUTELLIER[2];
[1]The Ohio State Univ., Columbus, OH; [2]Dept. of Psychology, Ohio State Univ., Columbus, OH

Abstract: Adolescence is an important period for the maturation of neurocircuitry and complex behaviors, including social interactions. However, mechanisms linking this parallel development remains unclear. The prefrontal cortex (PFC) is important for understanding this process, as structural changes in this region during adolescence shape social behaviors through direct projections to the ventral striatum (vStr) that regulate motivation and reward, as well as to the basolateral amygdala (BLA), which oversee threat assessment. During adolescence, a major maturational event in the PFC involves the gain of inhibitory power driven by parvalbumin-expressing (PV+) interneurons. This suggests that PV+ cells play a role in regulating the formation of local and long-range connections in the PFC that are crucial for the acquisition of the cautious social behavior that is typically seen in adult mice. This project looks to establish

that the adolescent maturation of prefrontal PV+ cells guide the maturation of social behaviors through changes in the activity of PFC-vStr and PFC-BLA circuits. Based on our preliminary data in mice, we propose that PV+ cells reorganize during adolescence to increase inhibition on the PFC-vStr reward processing pathway but decrease their inhibition on PFC-BLA threat assessment pathway. In this study, we chemogenetically inhibit PV+ neurons in the dorsal PFC of male and female PV:cre mice either throughout adolescence to disrupt maturation or starting early adulthood to investigate its effects on social behavior at adulthood using social motivation and social interaction paradigms. We then employ retrograde tracing and immunohistochemistry to count PV+ cell synapses on cells projecting to the vStr or BLA as a measure of change to PFC-vStr and PFC-BLA circuits resulting from the inhibition of PV+ cells. Our preliminary data indicate that the chemogenetic inhibition of PV+ cells during, but not after, adolescence leads to the inability of mice to achieve a typical adult-like behavioral phenotype, as indicated by an increased motivation to engage in social interactions that is characteristic of adolescent behavior. These results suggest that the reorganization of connections made by PV+ neurons in the PFC during adolescence could play an integral role in regulating the development of social behaviors.

Disclosures: K. Lin: None. **L. Coutellier:** None.

Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.12/A67

Topic: A.09. Adolescent Development

Title: Developmental Changes in Recognition Memory Depend on 3D Object Category and Object Orientation in Long-Evans Rats

Authors: *A. DEFINA[1], E. WILLIAMSON[2,3], S. SARKAR[2,3], S. BROWN[4], A. PANETTO[1], R. LEI[4], P. A. ROBINSON-DRUMMER[1,5];
[1]Neurosci. Program, Haverford Col., Haverford, PA; [2]Neurosci. Program, Bryn Mawr Col., Bryn Mawr, PA; [3]Neuroscience Program, Haverford College, Haverford, PA; [4]Psychology Dept., Haverford Col., Haverford, PA; [5]Psychology Department, Haverford College, Haverford, PA

Abstract: Novel object recognition (NOR) is a cognitive process that allows animals to recognize previously encountered stimuli. Recognition is demonstrated in humans and animal models, with variations used to explore memory ontogeny. Rodents prefer to explore a novel object over a familiar object (NOR) or familiar objects in novel locations (NOL). Additionally, animals' group similar objects into categories (ObjCat) allowing efficient responding to new exemplars without extensive previous experience. Research has been conducted on categorization of 2D objects in rodents, but little research has been done on the categorization on 3D objects. Further, how the specific 3D features contribute to the developmental emergence of recognition memory variations is not well characterized. The current project extends previous work by examining the contributions of object category and 3D orientation to learning in adult

and weanling rats. Our results reveal that after a 5min interval, juvenile rats at postnatal day (PD)23 showed stronger novelty memory when 3D objects had a *spatially-orientable feature* (e.g. irregular trapezoid with one pointed side; ORI) relative to *non-orientable objects* (e.g. a radially symmetrical cone; NonORI). This was not due to an inherent preference for the ORI or NonORI object as no significant object preference was observed in the object preference test. In periadolescent (PD35) pups, 3D Object categorization learning was observed when there was a 5min retention between sampling the category exemplars and testing with one novel object from a *novel category* and one *novel object* from the original *familiar category*. However, because PD35 pups failed to distinguish between objects from the same category when presented at once in an oddity task, periadolescent pups are likely not using category-based methods to show learning (i.e. using NOR strategies to show novelty preference). Adult rats did show both a preference for novel category objects in the oddity task and the object categorization task suggesting object categorization emerges between PD35 and PD60 in rats. To explore the cortical contributions of this learning, cFOS in the adult dorsal medial prefrontal cortex was measured but revealed no differences in activation based on learning tasks. These results suggest that 3D object category and orientation may influence emergence of recognition memory behavioral profiles during development. Additional analysis of cortical (e.g. ventral medial prefrontal cortex) and hippocampal contributions to learning are required to further elucidate the neurobiological underpinnings of this memory ontogeny.

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Poster

PSTR004: Adolescent Development: Animal Models

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.13/A68

Topic: A.09. Adolescent Development

Support: Undergraduate Research Scholarship by the OSU College of Arts and Sciences

Title: Navigating the Social Maze: Understanding the Impact and Restoration of Social Deficits in Mice through Early Isolation and Regrouping

Authors: *S. VARMAN, L. COUTELLIER;
Dept. of Psychology, Ohio State Univ., Columbus, OH

Abstract: Social isolation during early life is known to induce aberrant social interactions in adulthood. Previous investigations in mice have elucidated a critical developmental window of postnatal day (PD) 21 to 35 during which the absence of social interaction leads to the formation of these deficits, which no social regrouping afterward can restore. The conventional approach to studying social deficits and regrouping effects has primarily relied on the three-chamber sociability test, focusing narrowly on sociability, measured by time spent sniffing a cup

containing an unfamiliar peer, as a singular variable. Therefore, a complete understanding of the multifaceted nature of sociability and the impacts of social regrouping is lacking. Here, we provide an in-depth analysis of the behavioral consequences of early social isolation and subsequent social regrouping, employing a behavioral assay capable of monitoring various social behaviors. We used 3 experimental groups including: (1) mice that remained group-housed (GH) from PD21 to completion of data collection at PD67; (2) mice that were single-housed (SH) from PD21 to PD67; and (3) mice that were single-housed from PD21 to PD44, and socially regrouped (SR) from PD44 to PD67. Social behavior was investigated on PD67 using a test that allowed each mouse to freely interact with an unfamiliar mouse for 5 minutes. The following behaviors were hand-scored using the BORIS software: anogenital sniffing, nose-to-nose sniffing, other body sniffing, following, approaching, allogrooming, escaping, climbing over, and crawling under. Our comprehensive analysis of social behavior indicates that SH mice displayed hypersociability: compared to GH mice, SH mice exhibited a greater frequency and duration of anogenital sniffing, other body sniffing, and following behaviors. Social regrouping fully restored these three behaviors. This pattern was not found for any other social behaviors recorded. Altogether, our findings challenge the notion of irreversible social deficits following early social isolation and underscore the importance of considering the complexity of social behavior dynamics. Our study offers a novel perspective on the potential of regrouping interventions to mitigate some social deficits induced by early social isolation and promotes further investigations into the mechanisms underlying social behavior modulation. Future work involves correlating the identified behavioral effects with quantitative changes in prefrontal cortex parvalbumin interneurons and perineuronal nets.

Disclosures: S. Varman: None. **L. Coutellier:** None.

Poster

PSTR004: Adolescent Development: Animal Models

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Program #/Poster #: PSTR004.14/A69

Topic: A.09. Adolescent Development

Support: Spring 2024 BGSU Center for Undergraduate Research and Scholarship
Summer 2024 BGSU Center for Undergraduate Research and Scholarship

Title: Periadolescent Blue Light Exposure and Brain Development

Authors: *D. MESZAROS, V. R. RIESGO, J. WILLING;
Psychology, Bowling Green State Univ., Bowling Green, OH

Abstract: Nighttime exposure to blue light has been shown to disrupt circadian rhythms, neural functioning,and cognitive behavior. Blue light exposure in rats can alter learning and memory and can affect pubertalonset and sexual behavior. However, most of the work on the effects of blue light have focused on adultmale subjects. Given the near ubiquitous use of blue light-

emitting electronic devices, an emergingconcern is the effects of blue light on the developing adolescent brain in both male and female subjects. Inthe present study, periadolescent (P25-55) male and female Long Evans rats were exposed to blue lightfor 6 hours per night. In early adulthood (P60), subjects underwent a battery of tests to assess anxiety-likebehavior, exploratory behavior and hippocampal-dependent memory. Brain tissue was then collected atP90, and prefrontal cortex and hippocampal sections were nissl-stained and immunohistochemicallystained with MAP-2. Preliminary results show significantly altered exploratory and anxiety-like behaviorin the elevated plus maze and open field testing in blue light-exposed subjects. These results suggest thatadolescent blue light exposure may alter neural development, leading to an increased susceptibility toanxiety in adulthood in both sexes. These results add to the current literature by assessing the effects ofblue light specifically during adolescence in male and female subjects and suggest the need forsubsequent research on the extent to which chronic blue light can exert long-term effects on the brain andbehavior.

Disclosures: D. Meszaros: None. **V.R. Riesgo:** None. **J. Willing:** None.

Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.15/A70

Topic: A.09. Adolescent Development

Title: Interactions between prolonged exposure to high fat diet and social isolation through adolescence on inflammation, behavioral flexibility, and pain sensitivity in Long Evans rats

Authors: I. CAMPUZANO, L. ESTRELLA, M. RICE, E. SANCHEZ, E. MCCURRY, E. JANCOLA, E. KRANTZ, G. DELICH, ***P. M. BAKER**;
Psychology, Seattle Pacific Univ., Seattle, WA

Abstract: Prior research has established a role for both social isolation and exposure to high fat Western diets in altering a range of behaviors from reduced memory performance to increased depression-like behaviors. The present study scrutinizes the interplay among these variables during the peri-adolescent developmental phase, utilizing Long-Evans rats as the experimental model. Our overarching hypothesis is that rats exposed to either social isolation, a high-fat diet, or both will result in heightened pain sensitivity, diminished cognitive flexibility, and increased neuroinflammatory responses within brain regions implicated in sociability, cognition, memory, and pain processing. Behavioral flexibility will be assessed using a maze-based strategy switching task where animals are required to switch between allocentric and egocentric strategies. Pain sensitivity evaluations were conducted at three time points throughout the interventions using the manual Von Frey test. Subsequently, neuroinflammatory markers were assayed upon study completion to elucidate the presence of neuroinflammatory responses within select brain regions such as the somatosensory cortex, nucleus accumbens, prelimbic cortex, and hippocampus. A General linear model analysis was employed to detect disparities in pain

sensitivity or behavioral flexibility among sex, diet, and housing conditions. Preliminary results indicate that no statistically significant differences in pain sensitivity were observed across experimental groups when controlling for weight. However, upon omitting weight as a covariate, the sex condition emerged as significantly different in terms of pain tolerance, with males exhibiting greater tolerance compared to females ($b = -78.12$, $p < 0.03$, 95% CI [-142.16, -14.08]). Additionally, housing conditions exerted a notable difference in pain tolerance, with group-housed rats displaying higher pain tolerance compared to their relative group of socially isolated rats ($b = 78.11$, $p < 0.04$, 95% CI [14.07, -142.16]). Additional analysis will determine whether differences in behavioral flexibility are also present and further, whether interactions between levels of astrocyte, or microglia activation mediate observed effects on pain and behavioral flexibility. Overall, initial results indicate that social isolation through adolescence can increase pain sensitivity in adulthood with females being especially susceptible.

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Poster

PSTR004: Adolescent Development: Animal Models

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Program #/Poster #: PSTR004.16/A71

Topic: A.09. Adolescent Development

Support: CIHR Grant PJT-189943

Title: Exploring the impacts of adolescent nicotine vaping exposure on mood and anxiety pathophysiology in the amygdala-striatal network

Authors: *M. MACHADO, M. DEVUONO, M. SARIKAHYA, M. YOUSSEF, K. ZHAKSYLYK, T. UZUNESER, E. PÉREZ-VALENZUELA, M. DE FELICE, J. Y. KHOKHAR, W. J. RUSHLOW, S. R. LAVIOLETTE;
Dept. of Anat. and Cell Biol., Univ. of Western Ontario, London, ON, Canada

Abstract: Adolescence is a critical period of neurodevelopment, vulnerable to disruptions from neurotoxic substances, such as nicotine. Previous pre-clinical research has linked subcutaneous nicotine injections in adolescence, to increases in anxiety and depressive-related behaviours. Given the significant increase in the prevalence of adolescent nicotine vaping, understanding the neurological and behavioural consequences is crucial. Furthermore, evidence suggests disruptions within neuronal activity patterns and dysregulations in molecular signalling pathways. Specifically, alterations within the prefrontal cortex and hippocampus have been observed, however, we need to look at regions involved with emotional regulation, such as the nucleus accumbens (NAc) and basolateral amygdala (BLA). Previous studies have also highlighted the significant gap between male and female results, demonstrating a greater negative impact on male rats, with one possible explanation being differences in drug

metabolism in females. Therefore, this study aims to address these existing limitations by using an OpenVape model of nicotine inhalation, to closely mimic that of human nicotine consumption. Adolescent male and female Sprague-Dawley rats were placed in the vapour chambers and exposed to either commercially available 0% nicotine Stlth pods (vehicle) or 20% nicotine Stlth pods, for 10 minutes 3x per day for 10 consecutive days from postnatal day (PD) 35-44. At adulthood (PD>75), rats underwent behavioural tests to index emotional behaviour such as anxiety and depressive-like behaviours, that may be disrupted by adolescent vaped nicotine. *In-vivo* electrophysiology was then used to investigate neuronal adaptation in the NAc and BLA and molecular analyses in the regions of interest were also analyzed to further understand the mechanisms that may underly emotional dysregulation due to adolescent nicotine exposure. Preliminary findings indicate nicotine-induced hyperlocomotion during vape exposure with a noticeable decrease by day 10, suggesting the development of nicotine tolerance. Adult behavioural tests, *in-vivo* electrophysiology, and Western Blot analyses are ongoing. This study will also explore the unexplained sex differences, focusing on specific sex hormones, while investigating certain drug metabolites. The findings of the current study could provide valuable insight into the harms associated with adolescent nicotine exposure, aiming to improve the construct validity of vape models. Overall, this research aims to bridge the gap in understanding the specific impacts of vaping on adolescent neurodevelopment and behaviour.

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Poster

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NIMH Grant RO1-MH115049

Title: Sex-specific impact of early life adversity on startle behavior in mice

Authors: *A. M. DARLING[1], C. DEMAESTRI[2], K. G. BATH[3];
[1]Columbia Univ., New York, NY; [2]Sch. of Med., Tufts Univ., Boston, MA; [3]Psychiatry, Columbia Univ., New York, NY

Abstract: Sex-Specific Impact of Early Life Adversity on Startle Behavior in MiceEarly life adversity (ELA) is associated with an increased risk for stress-associatedpathology, including generalized anxiety disorder (GAD) and post-traumatic stressdisorder (PTSD), with females

having a two-fold risk of pathology development. A corefeature of these disorders is enhanced threat reactivity, including elevated startle. Startlerepresents a conserved endophenotype that is present in humans as well as in mice, andlikely shares common underlying neurobiological mechanisms. The maturation of brainregions implicated in the regulation of startle (e.g. extended amygdala) are sexuallydimorphic and the development of these regions have been found to be impacted byELA. However, whether these effects contribute to sex differences in risk for symptomexpression remains an open question and an important area of study to understand thebiological basis of sex differences in risk. Here, we model ELA using the resourcerestriction paradigm of limited bedding and nesting (LBN) from postnatal day (PD) 4 toPD 11 in mice. We tested for maturational changes in startle behavior across severaltime points coincident with maturation of regions supporting startle behavior –pre-adolescence, adolescence, and adulthood – to test effects of sex and ELA rearing onstartle behavior. Mice were startled at baseline, followed by being subjected to 10 tone(30 sec, 70dB, 12kH) shock (0.5mV) pairings. Twenty-four hours following tone-shockpairings, startle to a white noise was measured following both the conditioned tone(paired startle) and in the absence of the conditioned tone (unpaired startle). Results ofthese studies provide a greater understanding of both normative startle development inmale and female mice, and the impact of ELA on behavioral development. These studieswill both guide and constrain interpretations of ELA effects on the development of keybrain regions supporting startle behavior and their sexual differentiation overdevelopment. In sum, these studies have the potential to provide new insight into thedevelopment of behaviors supporting symptom expression, and to guide theenhancement of therapeutic approaches in treating stress-associated pathology in malesand females.

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Poster

PSTR004: Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: NIH Grant R01-MH086507
NIH Grant R01-MH127850

Title: Dysregulation of MD thalamic-evoked prefrontal GluN2A and GABA-mediated local field potential responses following early life adversity exposure at a discrete developmental period

Authors: *D. D. NEAL, K.-Y. TSENG;
Univ. of Illinois Chicago, Chicago, IL

Abstract: Exposure to early life adversity (ELA) can disrupt neural development and dysregulate neural circuits involved in cognitive and affective behaviors. Of importance to these

behaviors is the prefrontal cortex (PFC) which receives information from many brain regions including the mediodorsal thalamus (MD). In fact, the MD-PFC pathway is known to subserve cognitive functions such as working memory and social behavior, which are known to be compromised by ELA. Here we used *in vivo* electrophysiology to assess the functionality of the MD-PFC pathway and the extent to which is susceptible to disruption by maternal separation ELA. We found that the pattern of PFC local field potential responses to MD train stimulation is developmentally regulated through adolescence in both male and female rats. Specifically, a pattern of local field potential facilitation emerges at 10Hz that becomes attenuated following PFC infusion of the GluN2A antagonist NVP. On the other hand, MD train stimulation at 40Hz typically resulted in suppression of local field potential responses in the PFC that are insensitive to NVP. Instead, the 40Hz-evoked response is sensitive to GABA-AR blockade such that the level of local field potential suppression was markedly diminished by PFC infusion of picrotoxin. Following ELA, both the amplitude of GluN2A-mediated local field potential facilitation and the level of GABA-AR-mediated suppression were attenuated, specifically when the window of maternal separation occurred from P11 to P20. Recordings obtained from rats exposed to P2-10 maternal separation ELA revealed normal patterns of local field potential responses. Collectively, these results indicate that both excitatory and inhibitory mechanisms sustaining the MD thalamic-to-PFC transmission are developmentally regulated and sensitive to discrete periods of ELA exposure.

Disclosures: D.D. Neal: None. **K. Tseng:** None.

Poster

PSTR004: Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: REACH Grant
Matten Research Award

Title: Combined Methods of Early Life Stress and Inflammatory Challenge on PND22 Rats

Authors: *C. G. FORD, B. ATCHISON, C. RICHARDSON, M. J. HYLIN;
Psychological and Behavioral Sci., Southern Illinois Univ., Carbondale, IL

Abstract: In the modern social atmosphere, economic and other struggles related to raising children, are an unprecedented plague upon families. During the Covid-19 pandemic unemployment rates reached an all-time high, leading to significant financial distress for families, which in-turn led to many other psychosocial stressors. With prices on housing, food, and other common necessities increasing substantially, many mothers are forced to work multiple jobs, inevitably leading to child neglect, and a struggle with limited resources for their children. In the past couple of decades, both the immediate and delayed effects of early-life

stress as well as inflammation on immune function have seen an increase in research interest, specifically being examined in rat models. Studies related to these topics have had many interesting findings regarding maternal behavior, anxiety-like and depressive behaviors in offspring, decreased immune function, among others. Maternal separation (MS) and the limited bedding and nesting (LBN) paradigm have previously been examined in terms of the stressors themselves, with a select few studies examining the addition of lipopolysaccharide (LPS) to a single stressor, but we have yet to see a study that utilized these two stressors combined in addition to the inflammatory challenge of LPS. The current study examines just that, providing a uniquely comparable resemblance to the real-world stressors faced by today's youth. Behaviors are examined via the Morris Water Maze (MWM) as well as inflammatory and neurogenesis markers via immunohistochemistry, utilizing Iba-1 and doublecortin antibodies. The inflammatory challenge provided by LPS was expected to increase neuroinflammation, followed by a reduction in neurogenesis, along with deficits in spatial long-term memory as analyzed via the MWM, with the addition of stress leading to greater impairment. Keywords: early-life stress; maternal separation; limited bedding and nesting; inflammation challenge; neurogenesis; spatial long-term memory; microglia

Disclosures: **C.G. Ford:** None. **C. Richardson:** None. **M.J. Hylin:** None.

Poster

PSTR004: Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: NSF 1828305

Title: Molecular layer heterotopia of the neocortex and cerebellum are visible using microCT

Authors: J. POPP[1], S. TRINGALI[2], *R. RAMOS[3];
[1]New York Inst. of Technol., Westbury, NY; [2]New York Inst. of Technol. Col. of Osteo., Old Westbury, NY; [3]Biomed. Sci., New York Inst. of Technol. Col. of Osteo. Med., Old Westbury, NY

Abstract: Laminated cytoarchitecture in brain regions such as the neocortex and cerebellum emerges from the precisely timed proliferation and migration of neurons during development. Malformations and heterotopia in these brain regions arise from any perturbation affecting proliferation and/or migration and are generally accompanied by cognitive disability and seizures in affected patients. Molecular layer heterotopia (MLH) of the cerebellum and neocortex are characteristic of several human neurodevelopmental disorders and can be modeled in mice including Gpr56 knockout mice and C57BL/6J mice. Here we show that microCT is sensitive enough to identify neocortical and cerebellar MLH in iodine-stained brains of Gpr56 KO mice.

This technique can be used to complement other histological approaches to study MLH and associated changes in brain function.

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Poster

PSTR004: Adolescent Development: Animal Models

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Program #/Poster #: PSTR004.21/A76

Topic: A.09. Adolescent Development

Support: R01DA039062

Title: Impact of play deprivation in adolescence on maternal aggressive behavior in adulthood

Authors: *W. NIELSON[1], A. E. MARQUARDT[2], M. M. MCCARTHY[3];
[1]Pharmacol., Univ. of Maryland Baltimore Sch. of Med., Baltimore, MD; [2]Univ. of Maryland Med. - Inst. for Neurosci. Discovery, Baltimore, MD; [3]Dept. of Pharmacol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: As adolescents, many mammals engage in social play, which includes behaviors such as upright posture, pinning, and wrestling. Play is shown to be highly rewarding in a variety of species, and as such it is important to understand the benefits to conserving this behavior. By depriving adolescents of the ability to engage in rough and tumble play, we can observe and compare adult behavior between animals who played as adolescents and those who did not. Previously, from postnatal day 21 to postnatal day 45 (P21-P45), we placed pairs of male rats in cages fitted with fenestrated barriers which allowed the pairs to see, hear, smell, and touch each other but not to engage in rough and tumble play. Other pairs were housed in standard cages and the final group was single housed. Compared to standard-housed controls, single housed males showed significantly more aggression in adulthood during a resident-intruder assay and barrier-housed males showed a trend toward higher aggression. (PMID 36755666). In this experiment, we investigated whether this increase in aggression would also occur in females. We repeated the barrier housing and standard housing conditions with female rats whom we paired for breeding upon maturity. When each litter was aged P5 and P15, we placed unfamiliar, naïve males aged P50-P70 in the cage with the dams and their pups. We recorded this encounter to quantify displays of aggression from the dam toward the male, such as upright posture, lateral threats, strikes, keep downs, and clinch attacks. We found that barrier-housed dams did not engage in any one behavior more than control dams, though collapsing all behaviors into one measure revealed that on P5 barrier-housed dams trended toward higher aggression overall compared to standard-housed controls. (Welch's two sample t-test, n = 5 control dams, n=7 barrier dams, p= 0.055). These preliminary findings are consistent with the increased aggression observed in adult males that were deprived of play as adolescents (PMID 36755666). Future questions include whether dams' behavior will change for subsequent litters, as all dams used in this experiment

were naïve. We hope to spotlight the importance of socialization in adolescence and define the consequences of isolation for the isolated animals as well as other animals in their colonies.

Disclosures: **W. Nielson:** None. **A.E. Marquardt:** None. **M.M. McCarthy:** None.

Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.22/A77

Topic: A.09. Adolescent Development

Support: Good Nature Institute

Title: The role of oxytocin receptor in forced social interactions in juvenile mice

Authors: *R. OCHOA[1], E. A. HAMMOCK[2];
[1]Florida State Univ., Tallahassee, FL; [2]Psychology, Florida State Univ., Tallahassee, FL

Abstract: Species-typical social behavior regulates homeostasis throughout the lifespan. Oxytocin (OXT) and its receptor (OXTR) have a pronounced role in regulating social behavior and homeostasis in adults, but the evidence in developing brains is less well established. Additionally, reports have indicated social context influences behavior, such as the formation of dominant-submissive relationships, yet it is unknown if OXTR is related to this finding. Dominance is often measured with the tube test, wherein two mice are placed at opposing ends of a narrow tube. The mouse who makes it all the way through the tube is considered the "winner." When investigating the effects of genotype, traditional tube tests focus on win probability of each individual in a mixed-genotype dyad, but less is known about genotype impacts on behavior of the dyad when the participant genotypes do or do not match. In this study on juvenile mice, we evaluated the potential contribution of OXTR in social dominance behavior while controlling for sex and peer familiarity, in matched and mis-matched genotype dyads. We analyzed OXTR influence on individual win rates in mis-matched dyads and the contribution of sex, familiarity, and matched or mis-matched genotypes to dyad level test outcomes. To evaluate individual outcomes, we conducted the study using a 2x2x2 design with sex, familiarity (with cage mates or novel mice), and OXTR genotype (1 (heterozygous, HET), or 0 (knock-out, KO) copies of OXTR) as predictor variables for win frequency and win type (whether the opponent backs out or is pushed out of tube). To evaluate dyad level outcomes, we performed 2 x 3 x 2 ANOVA analysis, with sex, familiarity, and dyad genotype (HET:HET, HET:KO, KO:KO) as predictors for test duration and win type. We found that OXTR in adolescent mice appears to contribute to win probability in a sex-dependent manner with HET females, but neither genotype in males, winning more than chance. Furthermore, the HET genotype won more frequently by pushing the opponent out whereas KOs were more likely to win by their opponent backing out of the tube. Test duration was not predicted by dyad genotype, but we found that trials with unfamiliar mice took longer to finish, and were more likely to end by one participant backing

out. Our findings suggest social dominance behavior in the tube test of OXTR HET and KO mice is predicted by genotype only in females (KO more likely to lose), whereas dyad familiarity drives the type of win and total duration.

Disclosures: R. Ochoa: None. **E.A. Hammock:** None.

Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.23/A78

Topic: A.09. Adolescent Development

Support: NIH grant R01MH121706

Title: Does adolescent development of prosocial behavior depend on brain maturation?

Authors: *G. A. NEAL[1], A. A. PAL[1], A. I. BOWMAN[4], A. A. MORRISON[2], E. B. HUTCHINSON[3], K. M. GOTHARD[5];
[1]Neurosci., [2]Physiol., [3]Biomed. Engin., Univ. of Arizona, Tucson, AZ; [4]GIDP Neurosci., The Univ. of Arizona, Tucson, AZ; [5]Physiol., Univ. Arizona, Col. Med., Tucson, AZ

Abstract: Certain aspects of prosocial behavior develop and are refined during adolescence in both humans and non-human primates. We longitudinally monitored prosocial behavior in 6 adolescent (28-57 mo) and 2 adult (96-108 mo) male macaques in a social reciprocation task (Chang et al. 2011). We found that in parallel with physiological development, adolescent monkeys change their propensity to reward a social partner (5/6 adolescents, two-sample t-test, $p < 0.05$). One measure of physiological development, testicular volume, correlated with an increase in prosocial decision making (Spearman corr., $p < 0.05$; rho = 0.46). Behavior on the same social reciprocation task remained unchanged over the same period of time in adult controls, suggesting that prosociality matures during adolescence and remains subsequently stable. To explore the neurobiological foundation of these behavioral findings, we longitudinally monitored structural changes in the orbitofrontal cortex, amygdala, and the connection between them (the uncinate fasciculus), using diffusion tensor imaging (DTI). Preliminary results suggest connections between structural maturation in these brain areas and the observed behavioral changes. At the time of submission of this abstract DTI data collection was ongoing with the last longitudinal samples missing from our analyses.

Disclosures: G.A. Neal: None. **A.A. Pal:** None. **A.I. Bowman:** None. **A.A. Morrison:** None. **E.B. Hutchinson:** None. **K.M. Gothard:** None.

Poster

PSTR004: Adolescent Development: Animal Models

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.24/A79

Topic: A.09. Adolescent Development

Support: NIH Grant ZIA MH002928 (BA)

Title: Neural and behavioral dynamics of adolescent brain development in human and non-human primates.

Authors: *M. ANDUJAR[1,2], A. C. PARR[3], F. J. CALABRO[4], A. C. CUMMINS[5], S. R. WHITE[6], D. S. PINE[1], N. FOX[7], B. LUNA[8], V. A. ALVAREZ[9], C. A. NELSON[10], C. ZEANAH[11], L. LIUZZI[12], B. B. AVERBECK[13];
[1]NIH, Bethesda, MD; [2]NIMH, Bethesda, MD; [3]Ctr. for Neurosci. Studies, Univ. of Pittsburgh, Pittsburgh, PA; [4]Departments of Psychiatry and Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA; [5]LN NIMH NIH, Bethesda, MD; [6]NIMH, American Univ., Bethesda, MD; [7]Univ. Of Maryland, College Park, MD; [8]Dept. of Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [9]Lab. on Neurobio. of Compulsive Behaviors, NIH, Bethesda, MD; [10]Richard David Scott Chair in Pediatric Developmental Med. Res., Harvard Med. Sch., Boston, MA; [11]Tulane Univ., New Orleans, LA; [12]Emotion and Develop. Br., NIH, Bethesda, MD; [13]NIMH/NIH, Bethesda, MD

Abstract: Primate brain development begins during gestation and continues through early adulthood. Adolescence is particularly interesting as it coincides with the onset of many psychiatric disorders. Therefore, the study of the neurobiological mechanisms underlying typical and atypical adolescent brain development is crucial to understand the emergence of psychopathology. In this work, we present two studies that address this issue. The first study aims to elucidate neuroplasticity processes contributing to observed structural and functional developmental changes in human MRI studies. Additionally, it seeks to identify neural circuits where these processes influence reinforcement-based learning. To this purpose, we trained a cohort of adolescent and adult monkeys in a 2 armed bandit task and analyzed their behavior in the framework of reinforcement learning. In each session, monkeys learned which of two touchscreen options yielded the highest reward, with deterministic (first option consistently rewarded) and stochastic (first option rewarded 80% of the time) reward schedules. Adolescents learned slower than adults in deterministic schedules, and computational modeling suggested reduced learning from positive feedback in adolescents in stochastic schedules. Thus, our preliminary data support studies suggesting choice stochasticity and reduced reward/punishment sensitivity in younger individuals. Currently, we are collecting MRI, and histology data from monkeys to understand cellular-level processes underlying developmental brain changes observed in human MRI studies. Furthermore, we aim to clarify plasticity mechanisms explaining behavioral differences observed in this study. In the second study, we investigated the impact of early psychological deprivation on executive function development in human subjects, using dynamical systems theory. This framework predicts changes in neural dynamics, possibly related to the depth of attractor basins, with deeper basins associated with better performance. Analyzing task-related neural dynamics in children experiencing early deprivation from the Bucharest Early Intervention Project, we found older subjects had deeper basins around task-related EEG potentials during cognitive operations. Conversely, children with early deprivation exhibited shallower basins and poorer performance compared to controls. To summarize, these

results extend previous findings linking developmental brain changes to neural dynamics, emphasizing the importance of early experience for normative brain development.

Disclosures: M. Andujar: None. **A.C. Parr:** None. **F.J. Calabro:** None. **A.C. Cummins:** None. **S.R. White:** None. **D.S. Pine:** None. **N. Fox:** None. **B. Luna:** None. **V.A. Alvarez:** None. **C.A. Nelson:** None. **C. Zeanah:** None. **L. Liuzzi:** None. **B.B. Averbeck:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.01/B1

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

Support: Capes
FAPERJ
CNPq

Title: Regulation of the Type 1 Equilibrative Nucleoside Transporter by microRNA-124 and Exosomes

Authors: *I. OLIVEIRA[1], A. DOS SANTOS-RODRIGUES[2], R. SOARES LINDOSO[3], R. PAES-DE-CARVALHO[2], C. F. RONCONI[4], C. BASTOS PEREIRA LIGIERO[4];
[1]Neurobio., Federal Fluminense Univ., Niteroi, Brazil; [2]Neurobio., Fluminense Federal Univ., Niteroi, Brazil; [3]Rio de Janeiro Federal Univ., Rio de Janeiro, Brazil; [4]Inorganic Chem., Fluminense Federal Univ., Niteroi, Brazil

Abstract: Background: Adenosine, a neuromodulator found in several areas of the Central Nervous System (CNS), is important in several physiological and pathological events. It acts through the interaction with its receptors, which are divided in 4 subtypes: A1, A2A, A2B and A3. Its transport through the membrane is regulated by transmembrane proteins called equilibrative nucleoside transporters (ENTs), which were described in CNS into 4 isoforms, with ENT1/ENT2 being the predominant ones. MicroRNAs are non-coding RNAs that have been shown to play important regulatory roles, acting by an interaction with mRNA targets and interrupting the translation mechanism. A possible endogenous source of microRNAs would be the exosomes, small extracellular vesicles of endocytic origin produced in different CNS cell types.
Aim: To investigate if miRNA-124 regulates ENT1 expression and function and characterize the profile of vesicles released by chick retinal cultures.
Methods: All procedures were approved by the Ethics Committee on Animal Use of the UFF under protocol #1570300921. Mixed cultures of chick retina cells were obtained from embryos with eight days (E8) of development and transfected with miR-124 at different concentrations (0, 25, 50 and 100 nM) for 24h or 48h. Then, [3H]-Adenosine (Ado) uptake assay was performed to measure ENTs activity and Western Blot for ENT1 protein levels analyzes. Through

ultracentrifugation processes, we investigate if our cultures were able to produce exosomes, analyzing vesicles sizes by Dynamic Light Scattering (DLS) and their morphology by transmission electron microscopy (TEM).
Results: Exposure of cultures for 24 hours with miRNA-124 did not induce any significant change in [3H]-Ado uptake (CT 100%; miR-124 25nM: 93,2±6,63 n.s.; miR-124 50nM: 92,62±5,03 n.s.; miR-124 100nM: 93,38±4,46 n.s. n=3) or protein levels of ENT1 (CT 100%; miR-124 25nM: 90,51±14,93 n.s.; miR-124 50 nM: 114,16±36,6 n.s.; miR-124 100nM: 102,81±37,89 n.s. n=3). However, a longer treatment for 48 hours induced a significant reduction in [3H]-Ado uptake at miR-124 at 100nM (CT 100%; miR-124 100nM: 80,50±6,37 *p<0,05. n=3) and a trend of decreasing ENT1 protein levels at miR-124 (50 and 100nM) conditions (CT 100%; miR-124 50nM: 82,85±14,21 n.s.; miR-124 100nM: 58,81±12,89 n.s. n=3). DLS analysis revealed that extracellular vesicles have hydrodynamic sizes (D_H) in the range of 94–155 nm, with an average D_H of 129.2±25.7nm (n=4). TEM revealed a spherical morphology of these vesicles and an average size of 98,62 ± 71,33 nm (n=3).
Conclusion: These results suggest exosomes are released by retinal cultures and ENT1 as a potential regulatory target for miR-124.

Disclosures: I. Oliveira: None. **A. dos Santos-Rodrigues:** None. **R. Soares Lindoso:** None. **R. Paes-de-Carvalho:** None. **C.F. Ronconi:** None. **C. Bastos Pereira Ligiero:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.02/B2

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

Support: NIH Grant RO1aa030577

Title: Microglial and Neuronal Cross-talk in the Nucleus Accumbens

Authors: *S. SHARMA[1], I. ROQUE[1], C. GALBRAITH[1], H. A. WADSWORTH[2], L. FORD[2], L. HAWLEY[1], D. LANGFORD[3], S. LINDERMAN[1], P. E. WILLIAMS[2], E. B. TAYLOR[1], E. WHITE[4], J. A. HANSEN[1], J. T. YORGASON[5];
[1]Brigham Young Univ., Provo, UT; [2]Neurosci., Brigham Young Univ., Provo, UT; [3]BYU Neurosci., Brigham Young Univ., Provo, UT; [4]Neurosci., Brigham Young Univ., Holladay, UT; [5]Cell. Biol. and Physiol., Brigham Young Univ., Provo, UT

Abstract: Microglia, the resident immune cells of the brain, exhibit dynamic responses to signaling molecules. This study tests microglial responses to the following signaling molecules released in the NAc (nucleus accumbens): ATP (Adenosine triphosphate) and DA (dopamine), reactive oxygen species (ROS), and bacterial endotoxin lipopolysaccharide (LPS). There is extensive evidence supporting the role of ATP as a microglial chemoattractant inducing alterations in microglial motility and morphology. This study tested whether co-releasing DA

with ATP alters microglial responses to ATP signaling in the NAc. Despite immunohistochemical evidence supporting the expression of both DA and ATP receptors on microglia, we found that DA did not alter ATP-induced modifications of microglial morphology and motility. Surprisingly, ROS production in the NAc decreased dopamine release and altered microglial morphology, but had a minimal effect on ATP release. Since ROS are not influencing ATP release but are altering microglial morphology, this suggests the potential for a direct interaction between ROS and microglia. Finally, LPS induced crucial alterations in microglial morphology and increased both DA and ATP release in the NAc. LPS-mediated alterations in microglial morphology may help explain why pretreatment with LPS enhances methamphetamine-induced changes in dopamine reuptake in the NAc. We hope to further investigate the largely unexplored interactions between immune system activation and activity in neural reward centers in future studies.

Disclosures: S. Sharma: None. **I. Roque:** None. **C. Galbraith:** None. **H.A. Wadsworth:** None. **L. Ford:** None. **L. Hawley:** None. **D. Langford:** None. **S. Linderman:** None. **P.E. Williams:** None. **E.B. Taylor:** None. **E. White:** None. **J.A. Hansen:** None. **J.T. Yorgason:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.03/B3

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

Support: Howard Hughes Medical Institute

Title: Dopamine release sites possess a synaptic character that can enable spatiotemporally precise neuromodulatory signaling

Authors: *C. BULUMULLA[1], A. BEYENE[2];
[1]Howard Hughes Med. Inst., Ashburn, VA; [2]Janelia Res. Campus, Ashburn, VA

Abstract: Chemical chatter between neurons falls under one of two broad categories. In wired transmission, precise one-to-one communication occurs at spatially confined and well-defined synapses. On the other hand, volume transmission constitutes an open ended, relatively imprecise one-to-many communication that depends on passive diffusion of signaling molecules. This diffusion driven signaling mechanism obviates the necessity for tight spatial coupling. Dopamine is often considered to be the archetypal molecule from among the more than 100 neurochemicals that are thought to signal through volume transmission.
In a previous study, we showed that dopamine release is fast, gated by Ca^{2+} entry and released from varicosities that are enriched with some of the same active zone proteins employed by fast chemical synapses. The latest findings from our lab shows release competent dopamine boutons are often found spatially clustered and juxtaposed against the dendrites and soma of target

neurons. Correlative functional light microscopy and electron microscopy images revealed stereotypical synapses in axo-dendritic contact points at distal dendrites. We also observed axo-somatic and axo-dendritic associations in proximal dendrites, and interestingly, ultrastructural examination of these juxtapositions didn't appear to resemble classical synapse morphology. Importantly, axonal varicosities that lacked synaptic juxtaposition were release incompetent regardless of their vesicle content and Ca^{2+} influx. Thus, we concluded that synaptic juxtaposition to target neuronal processes is necessary for the release of dopamine from presynaptic boutons.
We next sought to establish if neurons that received synaptic dopamine input expressed dopamine receptors. Using RNA FISH, we showed that most of the neurons that received synaptic dopamine innervation at their soma were positive for D1 receptor (encoded by Drd1 gene) transcripts , suggesting that synapse formation by dopamine axonal processes is a non-stochastic and guided by yet to be understood molecular process. To get an improved insight into the spatiotemporal constraints of signaling by dopamine spillover, we performed sequential dual color cAMP and dopamine imaging. We observed that local fluctuations in cAMP levels in target postsynaptic processes were spatiotemporally gated by dopamine release. More importantly, spill-over from dopamine synapses did not modulate cAMP levels in neighboring peri-and extrasynaptic processes. These findings challenge volume transmission as currently understood and call for an improved model of neuromodulatory signaling between neurons.

Disclosures: C. Bulumulla: None. **A. Beyene:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.04/B4

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

Support: CAPES
FAPERJ
CNPq
UFF

Title: Regulation of the Equilibrative Nucleoside Transporter 1 (ENT1) expression and activity by lipid rafts in cultures of chick retinal cells

Authors: *A. DOS SANTOS-RODRIGUES[1], C. M. DOS SANTOS[2], S. B. SOUZA[3], R. PAES-DE-CARVALHO[4];
[1]Univ. Federal Fluminense, Niteroi, Brazil; [2]Oswaldo Cruz Inst., Oswaldo Cruz Fndn. (FIOCRUZ), Rio de Janeiro, Brazil; [3]Oswaldo Cruz Fndn. (FIOCRUZ), Rio de Janeiro, Brazil; [4]Neurobiologia, Fluminense Federal Univ., Niterói, Brazil

Abstract: Introduction: Equilibrative nucleoside transporters (ENTs) are transmembrane proteins known to mediate the nucleosides and some nucleobases flow through cellular membranes. The ENT1 and ENT2 isoforms are the most studied and are the prevalent ones in the Central Nervous System (CNS). Adenosine (Ado) is an important neuromodulator in the CNS and has roles in regulation of synaptic transmission and plasticity, cellular proliferation and differentiation, and is also involved in neurodegeneration and cell repair processes. ENTs have very important functions in CNS purinergic signaling, but our understanding on their regulation is still restricted. Lipid rafts are specialized membrane microdomains enriched in cholesterol, glycosphingolipids and specific proteins. These microdomains act as platforms for signaling molecules and can regulate several cellular processes such as intracellular trafficking and cellular signaling pathways. Objective: Our aim in this work was to investigate the association between the activity of ENT1 and the cholesterol-rich domains in cultures of chick retinal cells using methyl-beta-cyclodextrin (MBCD), a lipid raft disruptor. Methods: We measured cellular viability, cholesterol content, [^{3}H] Adenosine uptake, western blot and biotinylation in mixed cultures of chick retinal cells. All procedures were approved by the UFF's Animal Ethics Committee (protocol 1570300921). Results: Firstly, treatment of mixed cultures with MBCD (5 mM) for 45 minutes did not change cellular viability (90.7 ± 3.7 %, p=0.8498), whilst higher concentrations of MBCD (10 mM and 20 mM) significantly decreased cellular viability (67.7 ± 9.6%, p=0.0170; 18.7 ± 5.3%, p<0.0001). We observed a depletion of cholesterol content of the cells (55.5 ± 4.6%) and an increase of cholesterol content of extracellular medium (625 ± 25%) with treatment of cultures with MBCD (5 mM). We also found that treatment with MBCD (5 mM) for 45 minutes significantly decreased [^{3}H] Adenosine uptake (50.5 ± 11.0%, p<0.05). In addition, there was a tendency to increase the global expression of ENT1 with treatment with MBCD (5 mM), but this difference was not significant. Using biotinylation assays, it was possible to observe, a decrease in the expression of ENT1 in the cell membrane with the same treatment (27.8 ± 1.8%). Conclusions: These results show a possible interaction of ENT1 and membrane cholesterol, which can play an important role in regulation of this nucleoside transport activity at the cell membrane.

Disclosures: A. dos Santos-Rodrigues: None. **C.M. dos Santos:** None. **S.B. Souza:** None. **R. Paes-de-Carvalho:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.05/B5

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

Support: NIH Grant MH105094
FAU OURI Grant

Title: Sex-dependent alterations in nucleus accumbens dopamine release during juvenile social interaction: Impact of the neuropsychiatric disorder-associated DAT Val559 variant model

Authors: *T. WELLS[1], A. STEWART[2,3,4], C. MEINKE[1,5], R. D. BLAKELY[1,4];
[1]Biomed. Sci., Florida Atlantic Univ., Jupiter, FL; [2]Neurosci. & Pharmacol., Univ. of Iowa, Iowa City, IA; [3]Biomedical Science, Florida Atlantic University, Jupiter, FL; [4]Stiles-Nicholson Brain Institute, Jupiter, FL; [5]International Max Planck Research School for Synapses and Circuits, Max Planck Florida Institute for Neuroscience, Jupiter, FL

Abstract: Dysfunction in dopamine (DA) signaling has been linked to social deficits associated with disorders such as autism spectrum disorder (ASD). The DA transporter (DAT) variant Ala559Val (Val559) has been identified in individuals diagnosed with autism spectrum disorder, a disorder characterized by altered social behavior. The DAT Val559 substitution results in anomalous DA efflux that leads to sex-biased behavioral phenotypes in mice expressing the variant. Prior work in the Blakely lab using DAT Val559 mice noted deficits in social dominance and sociability in male DAT Val559 mice, phenotypes that are absent in females. Here, we evaluated the propensity for active social approach and interaction with a novel juvenile social stimulus in adult WT and DAT Val559 mice of both sexes while monitoring DA dynamics in the nucleus accumbens (NAc) using a genetically encoded $GRAB_{DA}$ sensor (AAV9-hsyn-DA2m (DA4.4)). We focused on the NAc as DA release in this region has been shown to promote social interaction and is implicated in social preference, novelty, and reward. When animals were presented with a sex matched juvenile, DAT Val559 male mice displayed a reduction in active social interaction that was accompanied by a dramatic reduction in NAc dopamine release as compared to WTs. In stark contrast, female DAT Val559 mice exhibited increased exploration of the social stimulus mouse and, while the peak DA surge following first interaction did not differ significantly between DAT Val559 and WT females, DAT Val559 displayed a faster rise in DA signal. To verify sensor expression and accurate probe placement, we injected male and female WT and DAT Val559 mice with amphetamine (AMPH) and cocaine to trigger elevations in extracellular DA. We noted no effect of sex or genotype on AMPH-stimulated DA release in the NAc. However, cocaine-dependent DA elevations were enhanced in DAT Val559 males while traces from DAT Val559 females displayed a faster return to baseline relative to WT littermates. In addition, while DA elevations were observed in female WTs only during the initial interaction with the stimulus mouse, in DAT Val559 females, DA elevations persisted with repeated interaction. Our data support DA dysfunction in DAT Val559 NAc circuits involved in the control of sociability, which may relate to social behavior perturbations in disorders such as ASD and may be related to the pronounced sex bias observed in ASD diagnoses. Further investigation into the neural substrates underlying alterations in sociability in DAT Val559 mice should shed light on how aberrant DA release and clearance alters social interaction in a sex-dependent manner.

Disclosures: T. Wells: None. **A. Stewart:** None. **C. Meinke:** None. **R.D. Blakely:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.06/B6

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

Support: R01 DA053372/DA/NIDA NIH HHS/United States
P30 NS047101/NS/NINDS NIH HHS/United States

Title: Chronic fentanyl exposure decreases dopamine release in human midbrain organoids

Authors: *H. YAO[1,2], X. HU[3], J. WANG[3], H. YIN[3], G. G. HADDAD[3,4,5];
[1]UCSD, La Jolla, CA; [2]Department of Pediatrics, UCSD, La Jolla, CA; [3]Dept. of Pediatrics, UCSD, La Jolla, CA; [4]Department of Neuroscience, UCSD, La Jolla, CA; [5]Rady Children's Hospital, UCSD, San Diego, CA

Abstract: The Midbrain is the major source of dopamine (DA) in the human brain and plays a critical role in the reward process, and hence it orchestrates addiction in humans. In order to understand how DA neurons contribute to the formation of opioid tolerance and dependence in the reward pathways, we have generated human midbrain organoids (hMBOs) derived from induced pluripotent stem cells (iPSCs), which harbor DA neurons. iPSCs were aggregated into the embryoid body and subsequently forming the hMBOs which grow to around 500 μ;m by day 30. Immunohistochemistry confirmed that hMBOs is composed of major human midbrain cell types during development, including neural stem cells that express midbrain floor plate marker FOXA2 and the transcription factor associated with patterning of ventral midbrain Otx2. We also detected the immunoreactivity of microtubule-associated protein 2 (MAP2), a postmitotic neuronal marker, thyroxine hydroxylase (TH), a marker of DA neurons, and GABA, a marker of GABA neurons in the outermost layers of the hMBOs. These data indicate that our hMBOs recapitulate the human midbrain environment, especially the development of dopaminergic system. Using Liquid Chromatography with tandem mass spectrometry (LC-MS/MS) technology, we studied DA release in hMBOs with or without the treatment of fentanyl (FTY). Our results show that DA release was detectable in hMBOs as early as at 30 days after embryoid body formation in hMBO under normal culture conditions. The DA release gradually increases at Days 60, 90 and 120 in hMBOs, suggesting that DA neurons mature over time during development. In the experimental groups, hMBOs were incubated with FTY for 30 days at various concentrations of 0.3, 1 or 3 uM. After that, FTY was withdrawn and hMBOs were cultured in normal culture media for the following three months. Our results demonstrate that FTY, dose-dependently, decreased DA release when measured at the end of FTY incubation (Day 30), demonstrating that FTY specifically altered the biological process of DA production and release in DA neurons in hMBOs. This DA depletion effect of FTY continues to be seen at day 60, 90 and 120, months after FTY withdrawal, although the DA release gradually recovered to normal by day 120, especially in the hMBOs treated with the lowest FTY concentration. Therefore, our hMBOs system proves to be an appropriate and useful tool for understanding the mechanisms of opioid addiction.

Disclosures: H. Yao: None. **X. Hu:** None. **J. Wang:** None. **H. Yin:** None. **G.G. Haddad:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.07/B7

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

Support: ANR-20-CE16-0003-01

Title: Deciphering the molecular mechanisms involved in ATP release by astrocytes using biosensors

Authors: *N. AHMADI[1,2], V. COMPAN[1,2], F. A. RASSENDREN[1,2];
[1]IGF U.Montpellier CNRS, INSERM, Montpellier, France; [2]LabEx Ion Channel Sci. and Therapeut., Montpellier, France

Abstract: Adenosine triphosphate (ATP) is an extracellular signaling molecule that acts on two main classes of membrane receptors, metabotropic P2Y receptors and ionotropic P2X receptors. In the central nervous system, purinergic receptors are involved in diverse functions such as modulation of synaptic transmission or neuron-glia communication. Yet, the mechanisms underlying ATP release are still poorly characterized and are likely diverse. Our aims are to identify the molecular mechanisms involved in ATP release by astrocytes in normal and pathological conditions. Our hypothesis is that Volume-Regulated Anion Channels (VRAC) encoded by the Leucine-Rich Repeat Containing 8 (LRRC8) family of protein could be involved in the release of ATP by astrocytes. Indeed, i) several studies demonstrated the presence of VRAC in astrocytes; ii) sustained neuronal activity can result in local change of extracellular osmolarity that can activate VRAC; iii) our preliminary results suggest that LRRC8 channels can release extracellular ATP. To investigate whether LRRC8 channels are involved in ATP release by astrocyte we combined the use of genetically encoded fluorescent ATP/ADP biosensor (ATP_{GRAB}) with RNAi strategy. We first determine whether lowering extracellular osmolarity can results in ATP release from astrocyte. Astrocytes in primary culture were transduced with AAV encoding the ATP_{GRAB} sensor and extracellular ATP-evoked fluorescence was monitored using live video-microscopy Our results show that ATP and ADP evoked a dose-dependent increase in fluorescence with an EC50 of 900±0.9 nM and 134±13 nM respectively. Next, we perfused astrocytes expressing the ATP_{GRAB} sensor with extracellular solutions of 160 and 90 mosm, respectively. We observed that hypotonic solution induced a fluorescent signal which intensity was dependent on the osmotic force: the lower osmotic solution evoked the higher fluorescence. To evaluate the contribution of LRRC8 to hypotonic-evoked ATP release, we used a RNA interference strategy. Through lentiviral-mediated shRNA expression, we were able to knockdown the expression of LRRC8A, the mandatory subunit of LRRC8 channel, by approximatively 80% in primary astrocyte culture. We further show that in astrocyte expressing LRRC8A shRNA, hypotonic-evoked ATP release was inhibited by 29.43±1.9 % and 41.63±3.59 % in 160 and 90 mosm condition, respectively. Together, our results support that in astrocyte LRRC8 channels can trigger ATP release in hypotonic conditions. Whether LRRC8-evoked ATP release is due to a direct permeation of ATP through the pore or to an indirect mechanism remains to be established.

Disclosures: **N. Ahmadi:** None. **V. Compan:** None. **F.A. Rassendren:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.08/B8

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

Support: NIH IRP Project Number: 1ZIAHD000711-34

Title: Does the dopamine transporter contribute to dopamine uptake in the mPFC?

Authors: *D. VULLHORST[1], J. P. WELDAY[2], R. MURPHY[2], A. L. BUONANNO[2]; [1]NICHD/Eunice Kennedy Shriver Nat'l Inst. of Child H, Kensington, MD; [2]Section on Mol. Biol., Natl. Inst. of Child Hlth. and Human Develop., Bethesda, MD

Abstract: The medial prefrontal cortex (mPFC) is innervated by dopamine (DA) projections from the ventral tegmental area (VTA) that, unlike projections to the dorsal and ventral striatum, express low levels of the DA transporter DAT. Hence, extracellular dopamine in the mPFC has been suggested to be cleared instead by COMT-mediated degradation and NET-mediated uptake into norepinephrine fibers. However, we previously showed that stimulation of the Neuregulin/ErbB4 signaling pathway acutely increases extracellular DA levels by downregulating DAT activity, not only in the striatum but also in the mPFC, thus implicating DAT in regulating cortical DA (Skirzewski et al., 2018; PMID:28727685).The goal of the present study is to reassess DAT expression and function in the mouse mPFC using a combination of immunohistological, retrograde tracing and optogenetic / fiber photometry approaches. Consistent with earlier reports, we find that DAT immunoreactivity is low or absent in deeper layers V/VI DA axons of the prelimbic and anterior cingulate cortex (ACC). However, we observe that DAT is strongly expressed in highly tufted DA axons in layers I-III of the prelimbic (PrL) and ventral ACC subdivisions (vACC). Microinjections of Cre-dependent retrograde viruses into superficial layers of DAT-Cre mice identify a cluster of vACC-projecting DA neurons that are located in an area encompassing ventromedial portions of the substantia nigra (SN) in addition to the VTA, which raise the possibility that DAT+ DA projections to the mPFC originate in the SN rather than in the VTA. We are currently performing fiber photometry experiments in acute slices from DAT-Cre mice using genetically encoded DA sensors to assess the contribution of DAT to DA clearance in the mPFC.

Disclosures: D. Vullhorst: None. **J.P. Welday:** None. **R. Murphy:** None. **A.L. Buonanno:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.09/B9

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

Support: R01DA056547
SUNY-Seed Grant

Title: Estrous cycle-dependent catecholamine transmission in the nucleus accumbens and ventral bed nucleus of the stria terminalis

Authors: *R. BHIMANI[1], R. PAULY[2], J. PARK[3];
[1]Biotechnical and Clin. Lab. Sci., Univ. At Buffalo, Buffalo, NY; [2]Biotechnical and Clin. Lab. Sci., State Univ. of New York, Univ. at Buffalo, Buffalo, NY; [3]Univ. at buffalo-SUNY, buffalo, NY

Abstract: Increasing evidence has suggested a role of gonadal hormones in modulating central catecholamine (dopamine and norepinephrine) regulation. In particular, norepinephrine in the ventral bed nucleus of the stria terminalis (*v*BNST) and dopamine in the nucleus accumbens have been highlighted for their roles in encoding the valence of sensory stimuli as well as driving sexually specific drug-seeking behaviors. Importantly, both of these systems have been emphasized for their roles in methamphetamine use disorders. While the influence of estrogens on modulating dopamine in the nucleus accumbens has received considerable attention in recent years, the *v*BNST, which receives the densest norepinephrine innervation in the brain and is sexually dimorphic, is often overlooked due in part to its neurochemical and anatomical complexity. In this study, we used fast-can cyclic voltammetry, a neurochemical sensing technique, coupled with pharmacological manipulations to characterize the role of different stages (diestrus/proestrus and estrus) of the estrous cycle on norepinephrine and dopamine regulation (release and clearance) in freely cycling females rats and compared these findings to male rats. We further investigated how different stages of the cycle impact methamphetamine-induced modulation of both dopamine and norepinephrine regulation. Our results show opposing regulation of dopamine and norepinephrine dependent on estrous cycle stage, which correlates with distinct levels of estradiol. Furthermore we show estrus females have increased dopamine responses to methamphetamine, whereas non-estrous females show greater methamphetamine-induced norepinephrine transmission. These results provide the pre-clinical neurochemical framework necessary to establish the heightened sensitivity and greater drug seeking behavior in female methamphetamine users.

Disclosures: R. Bhimani: None. **R. Pauly:** None. **J. Park:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.10/B10

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

Support: Lundbeck Foundation R359-2020-2301
Lundbeck Foundation R303-2018-2896

Title: Dopamine transporter interactome; identification of p140Cap as a potential modulator of dopamine signaling

Authors: *J. COLL MARQUÈS, J. SCHMIDT, M. D. LYCAS, F. HERBORG, U. GETHER; Univ. of Copenhagen, Copenhagen N, Denmark

Abstract: Dopamine is an essential neurotransmitter that plays central roles in numerous brain functions, prominently modulating motor activity, reward processing, and cognition. Consequently, dysregulation of dopaminergic signaling underlies a spectrum of disorders encompassing cognitive decline, movement disorders, psychiatric conditions, and addiction. The reuptake of released dopamine into the extracellular space is tightly controlled by the dopamine transporter (DAT), crucial for the precise termination of dopaminergic signaling, ensuring proper brain function. A comprehensive understanding of the *in vivo* protein interaction network of DAT is key to identify unique features that are linked to dopamine neurotransmission and unraveling potential implications for the development of dopamine-related disorders. In our study, we mapped the DAT proteome via antibody-mediate affinity-purification mass spectrometry and identified p140Cap (Srcin1) as a novel DAT interacting partner. Subsequent validation via co-immunoprecipitation in mouse striatal lysates and co-localization in presynaptic buttons of dopamine neurons confirmed their interaction. However, the role of p140Cap in dopamine synapses remains unknown. To delve deeper, we selectively silenced p140Cap in dopamine terminals *in vivo* by employing a genetically modified mouse line (Pitx3+/IRES2-tTA) and stereotactical viral delivery of an shRNA against p140Cap in the Substantia Nigra. Utilizing fiber photometry, we investigated how p140Cap silencing affects dopamine dynamics in the dorsolateral striatum alongside video recording to assess locomotor behavior before and after amphetamine administration. Preliminary findings indicate that unilateral p140Cap silencing in substantia nigra dopamine neurons correlated with heightened hyperlocomotion after amphetamine administration. Our ongoing investigations will address the effects of bilateral silencing of p140Cap in substantia nigra dopamine neurons. By unravelling the intricate interplay between p140Cap and DAT, our research aims to gain further insight into dopamine signaling. This understanding holds significant promise for developing targeted interventions to modulate dopamine-related disorders.

Disclosures: J. Coll Marquès: None. **J. Schmidt:** None. **M.D. Lycas:** None. **F. Herborg:** None. **U. Gether:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.11/B11

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

Support: Fondecyt 1221030
Fondecyt 1161375
R01 DA038598

Title: Differential Recognition of Monoamines by Human Monoamine Transporters and Organic Cation Transporter 3.

Authors: *L. A. DINAMARCA[1], M. MARAMBIO[1], A. I. ROBLES[1], G. E. TORRES, Sr.[2], A. FIERRO[1];
[1]Organic Chem., Pontificia Univ. Catolica de Chile, Santiago, Chile; [2]Mol. Pharmacol. & Neurosci., Loyola Univ. Chicago, Chicago, IL

Abstract: The primary mechanism for terminating the actions of neurotransmitters such as dopamine (DA), serotonin (5HT), and norepinephrine (NE) is their reuptake by specific monoamine transporters (MATs). These transporters include the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine Transporter (NET). However, recent studies have revealed the involvement of additional proteins as non-specific transporters for the reuptake of monoamines. Organic Cation Transporters (OCTs) are non-specific transporters for cationic molecules like monoamines. Interestingly, a subtype of OCTs (OCT3) is present in monoaminergic brain areas and is involved in the reuptake of DA, 5HT, and NE. The structure of OCT3 was resolved in 2022 using Cryo-EM and submitted to the PDB as a free protein (7ZH0) or in a complex with inhibitors (7ZH6, 7ZHA). However, information regarding the recognition of monoamines by OCT3 is lacking. Dysregulation of monoamines has been linked to neuropsychiatric disorders like depression, drug addiction, attentional deficit with hyperactivity disorder, schizophrenia, Alzheimer's, and Parkinson's disease, among others. Until the discovery of OCT in the regulation of monoamine concentrations, these proteins were not considered when reuptake inhibitors were used. This highlights the relevance of OCTs in the monoaminergic system and as novel pharmacological targets. In this study, we aimed to investigate the recognition pattern of DA, 5HT, and NE by OCT3. To achieve this, we used homology modeling, docking studies, and molecular dynamic simulations by comparing the structures of DAT, SERT, and NET. We found that OCT3 has a different recognition pattern compared to specific MATs. Different substrates induce distinct conformational changes in OCT3. The electrostatic potential distribution across the different transporters showed that OCT3 is more positively charged than MATs. The channel shape of OCT3 also creates wider cavities across the transporter compared to MATs. To complement the previous analysis, we used MM-PBSA to determine that MATs and OCT3 display a differential energetic profile. The results showed that OCT3 can recognize DA, 5HT, and NE with different affinities. Finally, we're currently testing this observation using *the transporters' in vitro expression* for functional studies. All this new information could lead to the development of new molecules that can bind to both MATs and OCT3 increasing the response of conventional reuptake inhibitors for the treatment of associated pathologies.

Disclosures: L.A. Dinamarca: None. **M. Marambio:** None. **A.I. Robles:** None. **G.E. Torres:** None. **A. Fierro:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.12/B12

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

Support: VA BX 001149
VA BX004475
NIH R41MH113398
NIH 5R01MH120168

Title: A simple platelet biomarker is associated with symptom severity in major depressive disorder

Authors: A. GUNAY[1], A. LEOW[2], O. A. AJILORE[3], *M. RASENICK[4];
[1]Dept. of Psychiarty, Univ. of Illinois at Chicago, Chicago, IL; [2]Dept. of Bioengineering ; Dept. of Psychiatry, Univ. of Illinois Chicago, Chicago, IL; [3]Psychiatry, Univ. of Illinois Chicago, Chicago, IL; [4]U. Illinois Col. of Med., Chicago, IL

Abstract: Previous studies have shown that the heterotrimeric G protein, Gsalpha (Gsα) is, in contrast to healthy controls, ensconced predominantly in lipid rafts in subjects with major depressive disorder (MDD) and that translocation of Gsα from lipid rafts may be a viable peripheral biomarker for assessing clinical status. Gsα is distributed normally by freely moving between two membrane regions: non-raft regions and a specialized region rich in cholesterol (lipid raft). Once activated, Gsα dissociates from the receptor and undergoes a conformational change that enables interaction with the effector enzyme, adenylyl cyclase (AC). The interaction of Gαs with AC stimulates enzymatic activity, increasing production of cyclic adenosine monophosphate (cAMP). We hypothesize that increased accumulation of Gsα in lipid rafts is a biomarker for depression and that the translocation of Gsα from those rafts is a biomarker for clinical response to antidepressant.The objective of this study is to utilize potential differences in platelet membrane localization of Gsα in platelets between patients with mood disorders and healthy controls and the resultant PGE1-activated cAMP response to validate a biomarker for MDD. Blood samples (2x from each subject) were collected and biomarker values were compared with the severity of depressive symptoms. Symptom severity was assessed the Hamilton Depression Rating Scale (HAM-D) and Quick Inventory of Depressive Symptomatology (QIDS-C_{16}) with the PGE1 stimulated AC biomarker. QIDS-C_{16} values inversely correlated with the biomarker response. MDD subjects with mild-moderate symptoms had significantly lower PGE1 stimulated AC than asymptomatic MDD subjects or healthy controls ($p= 0.001$ and 0.002 respectively). MDD subjects with moderate depressive symptoms had the lowest biomarker responses (Fisher exact= 0.012). Our findings support that excessive accumulation of Gsα in lipid rafts is a biomarker for depression, that the translocation of Gsα from those rafts, as reflected by an increase in PGE1 stimulated AC, reflects the sustained increase in cAMP observed with successful antidepressant treatment in humans and rodents. This simple, high-throughput-capable assay may be a useful biomarker for assessing depressive symptoms and tracking clinical response to antidepressants or potentially any therapeutic

intervention for depressed individuals and can be used to create a platform for personalized medicine.

Disclosures: A. Gunay: None. **A. Leow:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KeyWise AI. F. Consulting Fees (e.g., advisory boards); Buoy Health, Otsuka USA, ATAI Life Sciences. **O.A. Ajilore:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KeyWIse AI. F. Consulting Fees (e.g., advisory boards); Embodied Labs, Otsuka, Sage Therapeutics, Blueprint Health. **M. Rasenick:** A. Employment/Salary (full or part-time):; Pax Neuroscience. 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.; Veterans Administration, NIH. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lundbeck. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pax Neuroscience. F. Consulting Fees (e.g., advisory boards); Compass Pathways.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.13/B13

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

Title: Sex-dependent effects of glucose on dopaminergic signaling in mouse brain slices

Authors: S. ZIMMERMAN, M. KOLANOWSKI, ***E. RAMSSON**;
Grand Valley State Univ., Allendale, MI

Abstract: Glucose is a simple monosaccharide that serves as the primary energy source within the brain. Recent studies show an association between dysfunction in glucose metabolism and dopamine malfunction. Other studies have focused on the effects on insulin on the dopaminergic pathway. However, since insulin can take up to three hours to reach peak levels within the cerebrospinal fluid, its concentration in the brain lags behind glucose changes. Little is known about direct effects of glucose changes on dopamine in the brain. Previous work in our lab shows that varying acute glucose exposure causes a change in maximum dopamine levels, release, and uptake in a sex-dependent fashion in the caudate putamen. Initial responses show males are more sensitive to hypoglycemic conditions while females are more sensitive to hyperglycemic conditions. Using fast-scan cyclic voltammetry, we measure the effects of varying levels of glucose on dopamine neurotransmission within the caudate putamen and nucleus accumbens in mouse striatal slices.

Disclosures: S. Zimmerman: None. **M. Kolanowski:** None. **E. Ramsson:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.14/B14

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

Support: Funding from NIAAA RO1 AA030577 to JTY
Noorda College of Osteopathic Medicine

Title: Zmp prodrug p39-induced ampk activation enhances accumbal dopamine function

Authors: *S. BAKER[1], R. CAMPBELL[2], H. A. WADSWORTH[3], J. T. YORGASON[4];
[1]Noorda Col. of Osteo. Med., Provo, UT; [2]Brigham Young Univ., Provo, UT; [3]Neurosci., Brigham Young Univ., Provo, UT; [4]Cell. Biol. and Physiol., Brigham Young Univ., Provo, UT

Abstract: AMP-activated protein kinase (AMPK) plays an important role in regulating metabolic processes in the cell and holds potential as a druggable target for metabolic disorders. Prodrug-39 (P39) serves as an exogenous activator of the AMPK pathway, composed of phosphorylated ZMP (5-aminoimidazole-4-carboxamide-ribotide), a known endogenous activator and AMP analog. ZMP functions to enhance cell metabolism, leading to increased muscle growth. However, the central effects of the drug remain unknown. AICAR is a well-characterized AMPK activator. However, some studies indicate that AICAR-stimulated AMPK activation yields relatively small effects that are highly variable, likely related to its low pharmacoavailabilty. Indeed, the considerable levels of AICAR required to induce AMPK activation may result in unintended effects and render it impractical as a pharmacological agent. The objective of our study was to investigate P39's pharmacological potential in activating the AMPK and dopamine pathways. This was achieved via ex vivo application of P39 on accumbal brain slices from adolescent and aged mice and measuring the effects of AMPK activation on evoked dopamine release. Neuronal uptake of P39 was observed through fluorescent imaging of the catalyzed nitrophenol group. P39 was found to increase DA release independent of age in a dose-dependent manner. Additionally, P39 enhanced cholinergic interneuron-induced DA release. These findings reinforce ZMP as a key modulator of AMPK-activated dopamine release. Maintaining appropriate levels of DA in the brain by AMPK activation has implications including the slowed onset of muscle atrophy due to normal aging and delayed cognitive deficits.

Disclosures: S. Baker: None. **R. Campbell:** None. **H.A. Wadsworth:** None. **J.T. Yorgason:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.15/Web Only

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

Support: CIC-U.M.S.N.H.-2024
ICTI-2024-Michoacán

Title: Effect of serotonin antagonists on sodium pump activity in rat cerebral cortex.

Authors: *R. MERCADO[1], M. FLORES-MÁRQUEZ[2], O. GUZMÁN-QUEVEDO[3];
[1]Univ. Michoacana, Tarimbaro, Michoacan, Mexico; [2]Univ. Michoacana, Morelia, Mexico;
[3]Inst. Tecnológico Superior de Tacámbaro, Tacámbaro, Mich., Mexico

Abstract: Serotonin (5-HT) is a classic neurotransmitter that has been associated withmultiple functions in the CNS such as sleep regulation, thermoregulation, sexualbehavior, eating behavior, etc. 5-HT also regulates the Na+/K+- ATPase activity.Previous work of our laboratory demonstrates that 5-HT interacts with the sodiumand potassium pump through serotonergic receptors. On the other hand, Inpreliminary studies it has been observed that 5-HT2 receptor antagonists have aninhibitory effect on the activity of the enzyme, although this effect has not beencompletely characterized, so in the present work the effect of 5-HT2 receptorantagonists (Mianserin, Ritanserine, Spiperone, Ketanserin and Cyproheptadine)on sodium pump activity was studied in cerebral cortex homogenate, in glial andneuronal membranes of the cerebral cortex of adult male rats. The results showthat there is an inhibitory effect on the activity of the enzyme in a dose-dependentmanner, as similar as an inverse agonism phenomena and possibly through the 5-HT2C receptor activation. The present results support the functional relationshipbetween neurons and glial cells as an example of cellular communication.Acknowledgements: Partially supported by: CIC-U.M.S.N.H., ICTI-Michoacän.

Disclosures: R. Mercado: None. **M. Flores-Márquez:** None. **O. Guzmán-Quevedo:** None.

Poster

PSTR005: Catecholamines and Purines

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.16/B15

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

Support: NIH Grant RO1aa030577

Title: Methamphetamine effects on microglia in the context of dopamine and ATP release

Authors: *H. WADSWORTH[1], C. GALBRAITH[2], L. FORD[3], L. A. HAWLEY[3], D. LANGFORD[4], C. SYME[3], S. LINDERMAN[1], N. SHEETS[1], E. WHITE[3], E. B. TAYLOR[1], M. BURRIS[1], J. A. HANSEN[1], J. T. YORGASON[5];

[1]Brigham Young Univ., Provo, UT; [2]Brigham Young Univ., Provo, VT; [3]Neurosci., [4]BYU Neurosci., [5]Cell. Biol. and Physiol., Brigham Young Univ., Provo, UT

Abstract: Microglia are monocyte derived immune cells and exhibit complex signaling behavior that include phagocytic activity to threats and prolonged neuronal activity. ATP (adenosine triphosphate) is a known chemoattractant for microglia, and ATP is released from dopamine terminals, a major target for psychostimulants (such as methamphetamine). However, it is unknown how microglia chemotaxis is influenced by methamphetamine. Methamphetamine application impaired dopamine release and reuptake and had similar effects on ATP. Acute methamphetamine decreased microglia ramification and slowed down ATP induced chemoattraction. Morphological changes of microglia with methamphetamine is dependent on ROS, as shown through TEMPOL co-application preventing microglial morphology changes with acute methamphetamine. Mice injected with methamphetamine had increased expression of ROS associated proteins compared to saline injected controls. Also, repeated methamphetamine exposure increased microglial ramification compared to saline treated mice and saw a change in ATP induced chemoattraction. Methamphetamine treated animals had little to no change in the acute effects of methamphetamine on DA/ATP release as well as on microglial morphology. Yet methamphetamine injected animals had attenuated glucose oxidase effects on dopamine release compared to saline injected controls. By understanding how neuronal outputs affect microglia activity in the context of psychostimulant use we can better parse out how the mechanisms of addiction are connected to immune system function. These experiments also help to show the connection between methamphetamine, ROS and immune system activation. To ensure scientific rigor, analyzers were blinded for microscopy and electrochemistry analysis, and statistics, sample sizes and replication was specifically designed to verify results.

Disclosures: H. Wadsworth: None. **C. Galbraith:** None. **L. Ford:** None. **L.A. Hawley:** None. **D. Langford:** None. **C. Syme:** None. **S. Linderman:** None. **N. Sheets:** None. **E. White:** None. **E.B. Taylor:** None. **M. Burris:** None. **J.A. Hansen:** None. **J.T. Yorgason:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.01/B16

Topic: B.03. Ion Channels

Title: Pharmacological depletion of PIP_2 affects adrenergic modulation of $Ca_v2.2$ calcium channels.

Authors: *M. NEGRETE RUIZ[1], E. M. CASTRO RODRÍGUEZ[2], H. CRUZBLANCA-HERNANDEZ[1];
[1]Univ. de Colima, Colima, Mexico; [2]Ctr. Universitario de Investigaciones Biomédicas, Univ. de Colima, Colima, Mexico

Abstract: In sympathetic superior cervical ganglion (SCG) neurons, the N-type Ca^{2+} current (ICa_N) is inhibited by α_2-AR receptors by a voltage-dependent (VD) mechanism, upon binding of Gβγ to the α_1-channel subunit. Besides, muscarinic M_1 receptors and AT_{1A} receptors use a PIP_2-depletion mechanism to suppress ICa_N by a voltage-independent way. It is unknown whether there is cross-linking between these two inhibitory mechanisms; namely, if PIP_2 depletion modulates the adrenergic inhibition of ICaN. Here, we used the PI4K-inhibitor, phenylarsine oxide (PAO), also the PIP_2 "scavenger" poly-L-Lysine (PLL) to address that question. Whole cell patch-clamp ICa_N recordings were performed in cultured SCG neurons. The VD inhibition of ICa_N was assessed by using the conventional three command pulse protocol. To ensure that PAO reduced the level of PIP_2, the M-type K^+ current was monitored as an endogenous biosensor. PAO (30 μM; 8 min) by itself reduced ICaN current density from 20 ± 2.1 pA/pF (n = 11) to 15.2 ± 2.7 pA/pF. Afterwards, SCG neurons were challenged with 20 μM of norepinephrine (NE). In PAO-free neurons NE reduced ICa_N by 75.4 ± 3.8%, whereas in cells pre-treated with the PI4K-inhibitor the magnitude of the adrenergic inhibition was attenuated to 29.8 ± 3.8 %. Moreover the facilitation ratio of ICa_N, in the presence of NE, was reduced from 2.24 ± 0.23 to 1.29 ± 0.04. Finally, ICa_N re-inhibition by Gβγ was slowed-down since in control cells the time constant of was τ = 57.2 ms, while in cells treated with PAO it was 82.6 ms. To confirm that the α_2-AR inhibition of ICaN requires of PIP_2, other group of SCG neurons were dialyzed by ~ 9 min with a pipette solution containing PLL (200 μg/ml; 3 kD), before the NE challenge. The PIP_2 scavenger reduced current density from 40.4 ± 4.3 pA/pF (n = 11), found in cells dialyzed with the standard internal solution, to 19.0 ± 2 pA/pF (n = 9). In contrast with PAO, PLL slightly reduced the α_2-AR inhibition from73.8 ± 3.5% to 66.2 ±3.6%. Nevertheless, PLL disrupted the VD-inhibition of ICaN since the facilitation ratio was reduced from 2.2 ± 0.24 to 1.3 ± 0.12. We suggest that level of PIP_2 modulates the VD- α_2-AR inhibition of ICa_N.

Disclosures: M. Negrete ruiz: None. **E.M. Castro Rodríguez:** None. **H. Cruzblanca-Hernandez:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.02/B17

Topic: B.03. Ion Channels

Support: NIH Grant R01-NS-105987
NIH Gant F31-DK-136279
Eberly Endowment Fund from PSUCOM

Title: Ghrelin Inhibits Voltage-Gated Ca^{2+}Channels in Gastric Vagal Afferent Neurons

Authors: *H. GOUDSWARD[1], V. RUIZ-VELASCO[2], S. L. STELLA, Jr.[3], G. M. HOLMES[4]; [1]Penn State Col. of Med. Neurosci. Grad. Program, Hershey, PA; [2]Anesthesiol., Penn State Col.

of Med., Hershey, PA; [3]Neural and Behavioral Sci., Penn State Univ. Hershey-College of Med., Hershey, PA; [4]Neural & Behavioral Sci., Penn State Univ. Col. of Med., Hershey, PA

Abstract: Ghrelin is an orexigenic gut peptide that acts as an endogenous ligand for the growth hormone secretagogue receptor type 1a (GHSR1a). Systemic ghrelin administration increases gastric motility and emptying, and while it has been shown that these effects are mediated by the vagus nerve, the cellular mechanism underlying these effects remains unknown. Therefore, the purpose of the present study was to investigate whether GHSR1a modulates voltage-gated Ca^{2+} currents in gastric vagal afferent neurons isolated from male Wistar rats (age≥8 weeks) using whole-cell patch-clamp electrophysiology. First, we demonstrated that ghrelin inhibits Ca^{2+} currents (Ec_{50}=7.93, maximal response=42.8 ± 5.0% Ca^{2+} current inhibition) in gastric vagal afferent neurons. We confirmed these effects were mediated by GHSR1a, as treatment with the GHSR1a antagonist (D-Lys3)-GHRP-6 significantly (p=0.0064) reduced the effects of ghrelin (Ca^{2+} current inhibition= 1.90 ± 2.5%, n=6) as compared to neurons exposed to vehicle (Ca^{2+} current inhibition= 35.8 ± 20.6%, n=6). We also evaluated whether GHSR1a inhibited Ca^{2+} currents through a voltage-dependent or voltage-independent pathway using a triple-pulse voltage protocol. Interestingly, we found gastric vagal afferent neurons can utilize either pathway, suggesting there are additional subpopulations that can be classified based on which mechanism they utilize. This is further supported by the fact that both PTX (n=8, p=0.0327) and YM-254890 (n=8, p=0.0269) significantly reduced ghrelin's effects on Ca^{2+} currents as compared to untreated neurons, which indicates GHSR1a can couple to both $G\alpha_{i/o}$ and $G\alpha_{q/11}$ in these cells. Overall, our findings suggest GHSR1a-mediated inhibition of Ca^{2+} currents contribute to ghrelin's regulation of gastric vagal afferents, though future studies are necessary to confirm this modulation is sufficient to alter gastric motility and emptying *in vivo*.

Disclosures: H. Goudsward: None. **V. Ruiz-Velasco:** None. **S.L. Stella:** None. **G.M. Holmes:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.03/B18

Topic: B.03. Ion Channels

Support: PICT 2021 0300 Jesica Raingo

Title: Impact of constitutive activity of D1R-like receptors on Ca_V3 functionality in a hyperexcitability models associated with epilepsy

Authors: *E. MUSTAFA[1], S. S. RODRIGUEZ[1], J. RAINGO[2];
[1]Multidisciplinary Inst. of Cell Biol., La Plata, Argentina; [2]Univ. of Connecticut, Farmington, CT

Abstract: Our aim is to study the neuromodulatory role of the constitutive activity of dopamine type 1 receptors (D1R-*like* receptors, comprising D1R and D5R) on Ca_V3 calcium currents in neuronal hyperexcitability models associated with epilepsy. Our current work is based on our recently published study (doi: 10.1111/bph.16006), which describes the functional impact of constitutive activity of D1R-*like* receptors on Ca_V3 calcium currents in hippocampal neurons. In this study, we demonstrated that the constitutive activity of D1R-*like* receptors chronically and selectively reduces ionic currents and gating mediated by $Ca_V3.2$ and $Ca_V3.3$, consequently decreasing the excitability of pyramidal neurons in the hippocampal CA1 region. Given that changes in both Ca_V3 functionality and D1R-*like* receptor activity have been linked to epileptic states, we propose to investigate the role of this activity in epilepsy-associated hyperexcitability. To execute our current project, we propose the following experimental strategy to model exacerbated neuronal excitability: using a gain-of-function variant of $Ca_V3.2$ associated with epilepsy (R1282W) in a heterologous expression system and in primary hippocampal neuron cultures. For manipulating the constitutive activity of D1R-*like* receptors, we will use preincubations with chlorpromazine, a previously validated inverse agonist of D1R-*like* receptors. Here, we present data from the expression of the wild-type (Wt) variant of $Ca_V3.2$ as well as the R1282W variant in HEK293T cells in the presence or absence of D5R and recorded macroscopic currents using the patch clamp technique. We observed that the current levels in cells expressing the Wt version and D5R tend to be significantly lower than in cells expressing Wt alone, validating our previous work. We also observed that cells expressing R1282W and D5R exhibit current levels not significantly different from cells expressing Wt alone. This result could indicate reduced sensitivity of the channel with the R1282W mutation to the constitutive activity of D5R. Indeed, when constructing current-voltage (I-V) relationship curves, we observed that for the Wt version, the basal current inhibition from -40 mV is maintained at ~70%, whereas this value is reduced to ~20-40% for the mutated $Ca_V3.2$ version. It is important to note that it was previously demonstrated that the R1282W version exhibits significantly higher current levels than the Wt version, and here we observe a trend towards this increase when comparing these two conditions. Currently, we are adjusting the conditions to achieve transfection of hippocampal neurons in culture with the $Ca_V3.2$ wild type and R1282W mutated versions.

Disclosures: **E. Mustafa:** None. **S.S. Rodriguez:** None. **J. Raingo:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.04/B19

Topic: B.03. Ion Channels

Support: NIH R01NS126247
Veterans Affairs I01-BX004938

Title: The role of α2δ-2 in functional nanodomain coupling in Parvalbumin-expressing neurons

Authors: *A. ELLINGSON[1,2], K. A. BEESON[3], E. SCHNELL[4,5];
[1]OHSU, Portland, OR; [2]Neuroscience Graduate Program, OHSU, Portland, OR; [3]Harvard Univ., Boston, MA; [4]Neurosci. Grad. Program, OHSU, Portland, OR; [5]Portland VA Healthcare, Portland, OR

Abstract: Calcium (Ca2+) influx into neurons via voltage gated calcium channels (VGCCs) is required for neuronal signal transduction and neurotransmitter release. VGCCs are composed of several different subunits, including α2δ proteins, and mutations in the genes that encode for α2δs can cause severe neurological disease. Previous studies have suggested that α2δs may play important roles related to VGCCs, including functional coupling of VGCCs to important machinery at both the pre- and post-synaptic membranes. At the presynaptic terminal, α2δs couple Ca2+ entry to vesicle release machinery and control the probability of release. In postsynaptic cells, α2δs might affect action potential afterhyperpolarization (AHP) by coupling Ca2+ entry to Ca2+ dependent potassium channels, which are responsible for the AHP and regulate cell firing rates. Studies of α2δs in brain circuits have been complicated by compensation between isoforms and the lethality of most double-isoform knockout mutants. However, the α2δ-2 isoform is selectively expressed by parvalbumin-expressing (PV+) inhibitory neurons, and genetic loss of α2δ-2 is not well compensated by other α2δ isoforms, as α2δ-2 knockout mice are severely epileptic and ataxic. Thus, the unique role of α2δ-2 in these cells provides an opportunity to study both how α2δ-2 contributes to neuronal function across the brain and to gain deeper insights into the roles of α2δs in neurons overall. Here, we will investigate the role of α2δ-2 in PV+ cerebellar Purkinje cells and hippocampal PV+ interneurons using electrophysiological recordings from WT and α2δ-2 KO mice. In cerebellar Purkinje cells, AHP amplitude is reduced and not sensitive to elevated concentrations of intracellular calcium channel buffering, consistent with a loss of functional nanodomain coupling of VGCC-mediated Ca2+ entry to potassium channels in α2δ-2 KO Purkinje cells. Preliminary studies in hippocampal PV+ cells from α2δ-2 KOs are also consistent with altered functional coupling. Circuit-level effects are being assessed with voltage clamped recordings, to determine whether the ratio of excitatory: inhibitory synaptic responses is changed in the dentate gyrus of KO mice. Together, these findings suggest that α2δ-2 may play critical roles in a variety of PV+ neurons and may provide clues about the roles of other α2δ isoforms in other neuron types across the brain.

Disclosures: **A. Ellingson:** None. **K.A. Beeson:** None. **E. Schnell:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.05/B20

Topic: B.03. Ion Channels

Support: CIHR
NSERC

Title: Macro-molecular protein complex of voltage dependent calcium channel gating neurotransmitter release in central synapses

Authors: *R. SAGHIAN[1], J. ARSENAULT[2], L.-Y. WANG[3];
[1]Univ. of Toronto, Toronto, ON, Canada; [2]SickKids Hosp., Toronto, ON, Canada; [3]Sickkids Res. Inst&Univ Toronto, Toronto, ON, Canada

Abstract: The intricate interplay of ion channels shapes the input-output of neurons, allowing them to communicate effectively. To ensure the spatiotemporal control of neurotransmission, voltage gated calcium channels are highly organized near active zones to drive fast and synchronous fusion. However, much remains to learn about the macromolecular complexes at release sites. In our quest to identify critical molecular substrates governing fast neurotransmission, we encountered a novel protein, which we will refer to as 'Protein Y', that has a well-established role in lipid metabolism, bone formation, and calcium absorption. Recently, it has also been implicated in malignant cancers, underscoring its pharmacological relevance. Surprisingly, its functions within neurons remain unexplored. Our study aims to uncover the noncanonical roles of Protein Y by investigating its involvement in the formation of macromolecular protein complexes that supports rapid synaptic transmission. We hypothesize that this complex dynamically responds to intracellular calcium level, facilitating the efficient release and reloading of neurotransmitters. In our study, using an antibody against Cav2.1, we pulled down associated proteins from the mouse cerebellum. Subsequent mass spectrometry analysis revealed that Protein Y consistently co-immonuprecipitated (co-IP) with Cav2.1 which was further validated by Western blots. Immuno-histochemical labeling demonstrated that Protein Y is highly colocalized with Cav2.1 within nerve terminals. Protein Y also co-IPed and colocalized with vGlut1, but not vGlut2.To investigate the direct interaction of Cav2.1 and Protein Y, each protein was tagged with FRET pair fluorophores. Through FLIM-FRET microscopy, we observed a substantial reduction in fluorescence lifetime indicative of direct interaction. To study the physiological role of Protein Y, we conducted paired patch-clamp recordings from the calyx of Held synapse where we delivered Protein Y into the presynaptic terminal and observed a reduction in the unitary amplitude of miniature excitatory postsynaptic currents (mEPSCs). These mEPSCs represent quantal responses to individual packets of glutamate released from synaptic vesicles, implicating the effect of Protein Y on vGlut activity for glutamate upload. Our findings suggest that Protein Y not only is an integral component of macromolecular complex with Cav2.1 to tether SVs for Ca2+-dependent fusion to release neurotransmitter, but also dynamically modulate glutamate concentration within SVs, both of which have significant implications for understanding synaptic transmission and plasticity.

Disclosures: **R. Saghian:** None. **J. Arsenault:** None. **L. Wang:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

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Topic: B.03. Ion Channels

Support: Deutsche Forschungsgemeinschaft, SFB1348, TP A03

Title: Neurexin binding dissociates auxiliary alpha2delta subunits from voltage-gated calcium channels

Authors: N. HOHAUS[1], C. REISSNER[2], *M. MISSLER[3];
[1]Inst. of Anat. and Mol. Neurobiology, Univ. of Muenster, Muenster, 48149, Germany; [2]Inst. of Anat. & Mol. Neurobiology, Univ. of Muenster, Muenster, Germany; [3]Univ. of Muenster, Muenster, Germany

Abstract: Presynaptic Ca^{2+} influx through voltage-gated calcium channels (VGCCs) triggers the release of neurotransmitter vesicles. Deletion of the cell adhesion molecules neurexins, essential presynaptic organizer molecules, has been shown to impair VGCC-dependent neurotransmitter release. While our previous studies have focused on regulating Ca^{2+} influx in these deletion mouse models, the physical relationship between neurexin molecules and VGCC subunits remains unknown. Here, we employed a nanobody-based co-precipitation system in heterologous cells expressing a human $Ca_V2.1$ (P/Q-type) Ca^{2+} channel fused to an intracellular EGFP epitope. Using a GFP trap, we observed the complex formation of the pore-forming α1 subunit together with auxiliary β and α2δ subunits as expected, but not directly with neurexin. However, we were able to demonstrate that neurexin binds via α2δ subunits, albeit weakly. We determined that interaction with α2δ subunits occurs via the extracellular LNS2-4 domains as well as the stalk domain of neurexins. Moreover, we observed that the scaffold proteins Mint1/2 facilitated neurexin binding to α2δ subunits by reducing their degree of glycosylation. In accordance, we found a preference for neurexin to bind the α2δ-3 variant which is generally less glycosylated than α2δ-1. Similarly, the overall binding of neurexin to α2δ was enhanced by reducing glycosylation of the stalk domain of neurexin, with the strongest binding observed when no glycosylation was allowed. Finally, both $Ca_V2.1$ ($\alpha1_A$) and $Ca_V2.2$ ($\alpha1_B$) pore-forming subunits demonstrated a binding preference towards the more heavily glycosylated α2δ-1 subunit compared to α2δ-3. Together, our data suggest an intricately regulated binding behavior of neurexins and VGCC subunits, possibly allowing neurexins to dissociate auxiliary α2δ subunits from their pore-forming subunits.

Disclosures: **N. Hohaus:** None. **C. Reissner:** None. **M. Missler:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.07/B22

Topic: B.03. Ion Channels

Support: LifeArc Ltd. PhD studentship
University of Reading PhD studentship

Title: The MIDAS motif of CACHD1 is important for CACHD1 expression and function as a $Ca_V3.1$ voltage-gated calcium channel modulator

Authors: *M. ROZNOVCOVA[1], T. DEUTSCH[2], M. K. PATEL[3], G. COTTRELL[1], G. STEPHENS[1];
[1]Univ. of Reading, Reading, United Kingdom; [2]Charlottesville, VA, ; [3]Univ. of Virginia Hlth. Syst., Charlottesville, VA.

Abstract: Voltage-gated calcium channels (VGCCs) play a crucial role in the regulation of intracellular calcium, and its dysregulation is associated with different disease states, including hyperexcitability diseases such as pain. α2δ auxiliary subunits of high-voltage-activated (HVA) VGCCs are targets for gabapentinoids, commonly used in pain management. However, low-voltage-activated (LVA) VGCCs are not modulated by α2δ. CACHD1 (calcium channel and chemotaxis receptor domain containing protein 1) was characterised as a modulator of Ca_V3, LVA VGCCs. Both α2δ and CACHD1 contain a MIDAS (metal ion-dependent adhesion site) motif within their von Willebrand Factor A (VWA) domains, previously shown to be essential for the trafficking and synaptic function of HVA VGCCs.
We investigated the effects of MIDAS motif mutations in CACHD1 on its expression and function as a modulator of $Ca_V3.1$ VGCCs in HEK293 cells stably expressing Myc-tagged CACHD1. Two CACHD1 MIDAS motif mutants; CACHD1-AAA (3 key residues mutated to Ala, D^{234}xGxS to AxAxA) and CACHD1-G236S (mimicking α2δ (DxSxS) MIDAS motif) were generated. Sub-cellular localisation of CACHD1 was assessed by immunocytochemistry, using live and fixed cell labelling (n=5). Expression levels of CACHD1 were characterised by western blotting and densitometry (n=5); statistical significance was determined using ANOVA (Tukey's post hoc test). CACHD1 modulation of $Ca_V3.1$ was characterised by patch clamp electrophysiology; statistical significance was determined using ANOVA (Bonferroni post hoc test) and two-tailed unpaired t-test.
CACHD1-wt and CACHD1-G236S were localised to the cell surface and intracellular vesicles, whereas CACHD1-AAA was localised to intracellular vesicles. In expression studies, a significant reduction in total CACHD1 levels was seen for CACHD1-AAA (22±6.8% vs CACHD1-wt, mean±SEM, $p<0.05$) with no significant change for CACHD1-G236S (93±4.2% vs CACHD1-wt, mean±SEM). CACHD1-wt and CACHD1-G236S significantly increased $Ca_V3.1$ current density and maximal conductance, while CACHD1-AAA caused significant reduction in $Ca_V3.1$ currents and maximal conductance.
Our findings highlight the essential role of the MIDAS motif in CACHD1, suggesting that, like the α2δ MIDAS motif, the CACHD1 MIDAS motif contributes to protein expression and CACHD1-associated modulation of $Ca_V3.1$ VGCCs. Modulation of Ca_V3 expression might have therapeutic utility for hyperexcitability diseases, including pain.

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grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; University of Reading.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.08/B23

Topic: B.03. Ion Channels

Support: 1R01NS125271

Title: Novel technique for optically controlling L-type calcium channel function shows signaling from dendritic spine to nucleus to control transcription and translation

Authors: *N. MANDELBERG[1], H. G. KHALED[2], R. W. TSIEN[3];
[1]Neurosurg., New York Univ. Sch. of Med., New York, NY; [2]Neural Sci., New York Univ., New York, NY; [3]Neurosci. Inst., NYU Grossman Sch. of Med., New York, NY

Abstract: Neurons perform a remarkable range of tasks by changing their physiology in response to external stimuli. L-type voltage gated Ca^{2+} (Ca_V1) channels are critical for plasticity because of their privileged role in regulating transcription and thus translation in response to depolarization. However, it is not clear how activation of synapses controls nuclear transcription up to hundreds of microns away. The coupling mechanism between synaptic activity and activation of gene expression predetermines the types of synaptic or electrical activity that can affect neurons' genetic programs. We developed a technique to optically isolate dendritic or somatic Ca_V1 activity using a photolabile Ca_V1 channel antagonist. We show that Ca_V1 channels act from dendrites to drive CaMKII-dependent activation of the powerful transcription factor CREB, synergizing with N-methyl-*D*-aspartate receptors (NMDARs), even in the absence of spikes. We also use this technique to show that Ca_V1 activity at dendritic spines drives the expression of the immediate-early gene c-Fos. These same synaptic molecules enable both mEPSPs and action potentials to signal to the nucleus. We find that Ca_V1 channels cooperate with NMDARs to drive signaling to the nucleus and gene expression from dendritic spines, and that activity from even a handful of spines can have impact on a neuron's transcriptional and translational programs.

Disclosures: N. Mandelberg: None. **H.G. Khaled:** None. **R.W. Tsien:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

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Guangdong Basic and Applied Basic Research Foundation (2023B1515040019 to BL)
Guangdong Project (2017GC010590 to BL)

Title: Precision control of intrinsic excitability homeostasis by subcellular L-type calcium channels

Authors: *Z. WEI[1], X. ZHANG[2], L. CHEN[3], L. HUANG[2], B. LI[4];
[1]Sun Yat-sen Univ., Guangzhou, China; [2]Dept. of Pathophysiology, Sun Yat-sen Univ., Guangzhou, China; [3]Zhongshan Sch. of Med., Sun Yat-Sen Univ., Guangzhou, China; [4]Zhongshan Sch. of Med., Sun Yat-Sen Univ., Guangzhou City, China

Abstract: The stability of neuronal circuitry depends on the homeostasis of neural firing properties, but how such plasticity is precisely regulated remains to be elucidated. Here we report that neocortical pyramidal neurons increase their FR and APD in order to adapt to a chronic suppression of activity. During chronic inactivity, somatic Ca_V1 channels in the soma are primarily closed, whereas dendritic Ca_V1 channels tend to be open. In the soma, the closed Ca_V1 channels recruit SAMD3 to the plasma membrane via protein-protein interaction, thereby reducing SMAD3 levels in the nucleus and downregulating the SMAD3-dependent transcription of *Kcnq3*, which encodes the $K_V7.3$ potassium channel. This reduction in $K_V7.3$ channels eventually leads to a homeostatic increase in the neuron's firing rate. Together with our previous finding that activation of Ca_V1 channels in dendritic spines engages the CaMKK-CaMKIV-Nova-2 pathway to regulate the alternative splicing of BK channels, which play a critical role in APD homeostasis, our findings reveal how Ca_V1 channels can regulate the homeostasis of both FR and APD simultaneously in a state-dependent, subcellular localization-dependent, and mechanism-dependent manner. This effect is physiologically relevant, as we found that homeostatic adaptation to chronic neuronal inactivity in the visual cortex led to a stronger innate defensive response to visual stimuli in freely moving mice. Our results provide a framework for understanding how the same protein ($Ca_V1.2$) residing in different states (closed versus open) and subcellular locations (the soma versus dendritic spines) can coordinately regulate critical cellular functions at the molecular, cellular, and behavioral levels. These findings have broad implications with respect to understanding the changes in these homeostatic mechanisms that underlie neurological disorders and for guiding the development of new therapeutic strategies designed to target these mechanisms.

Disclosures: Z. Wei: None. **X. Zhang:** None. **L. Chen:** None. **L. Huang:** None. **B. Li:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

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Program #/Poster #: PSTR006.10/B25

Topic: B.03. Ion Channels

Support: 5T32 NS077889
NS088555

Title: Long-term b cell depletion decreases spontaneous neuronal firing in the dentate gyrus of aged mice

Authors: *T. A. UJAS[1], N. TAVAKOLI[1], J. TURCHAN-CHOLEWO[2], P. I. ORTINSKI[3], A. M. STOWE[4];
[1]Univ. of Kentucky, Lexington, KY; [2]Dept of Neurol., Univ. of Kentucky, Lexington, KY; [3]Neurosci., Univ. of Kentucky, Lexington, KY; [4]Neurol., Univ. of Kentucky, Lexington, KY

Abstract: Background: Previously, we showed that B cells migrate into hippocampal regions and affect memory function after stroke in mice. The present study focuses on investigating the impact of circulating B cells on spontaneous hippocampal neuronal firing using wide-field calcium imaging as an indirect but accurate measure of action-potential generation within neurons. Methods: C57BL/6 synapsin-Cre/GCaMP6S$^{+/-}$ mice (n=21 total) were used (11 males; 10 females) in adult (4-8 mos.; n=10) and aged (10-18 mos.; n=11) groups. 12 untreated mice were used as baseline for spontaneous hippocampal activity, while 9 mice received 100µL (1mg/mL) anti-CD20 antibody (Genentech) injections over 3 days then weekly to deplete circulating B cell populations. After 3 weeks of B cell depletion, brains were extracted, sectioned into 300µm slices, oxygenated, and kept at 37ºC in aCSF, using an NMDG (N-methyl-D-glucamine) solution. Spontaneous neuronal activity in the CA1 and dentate gyrus (DG) of the hippocampus was recorded using wide-field calcium imaging. 1668 CA1 and 3403 DG cells were recorded in total. For each cell, a fluorescence trace was generated by averaging all pixels within ROI outline in each recording frame. The background signal was removed from each cell's fluorescence trace. Calcium transients were identified using a wavelet ridgewalking algorithm (MATLAB). All cellular analysis was conducted while blinded. We measured amplitude, event frequency and duration of calcium transients. Statistical analyses were performed in GraphPad Prism. The Kruskal-Wallis test with multiple comparisons was used to determine statistical significance. Results: B cell depletion in adult male and female mice did not significantly affect CA1/DG firing respective of WT naïve counterparts. However, when recording from aged male and female animals in the DG, we saw significant decreases in amplitudes with B cell depletion for both aged males ($p=0.0069$) and aged females ($p<0.0001$) compared to non-depleted age and sex-matched controls. Consequentially, B cell depleted cohorts exhibited an increased event frequency in the DG compared to WT females ($p<0.0001$) and WT males ($p<0.0001$), but this only occurred in the aged and not adult cohorts. Conclusion: Our initial experiments are critical to establish the potential role of B cells in hippocampal signaling during health and aging, with ongoing investigation into the impact of ischemic stroke coupled with B cell depletion in hippocampal neuronal activity. While this may help in understanding long-term cognitive decline after stroke, it will also inform for other CNS diseases and injuries characterized by an immunosuppressive phenotype.

Disclosures: **T.A. Ujas:** None. **N. Tavakoli:** None. **J. Turchan-Cholewo:** None. **P.I. Ortinski:** None. **A.M. Stowe:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

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Program #/Poster #: PSTR006.11/B26

Topic: B.03. Ion Channels

Title: Functional characterization of a Cav2.1 mutation linked to impaired homeostatic synaptic plasticity

Authors: *J. THOMAS[1], J. HAGEN[2], C. FRANK[2], A. LEE[3];
[1]Meharry Med. Col., Nashville, TN; [2]Univ. of iowa, Iowa City, IA; [3]Neurosci., Univ. of Texas, Austin, Austin, TX

Abstract: Homeostatic synaptic plasticity (HSP) involves a decrease or increase in synaptic output that compensates for sustained alterations in neuronal activity. Dysregulation of HSP is implicated in a variety of neurological and neuropsychological disorders, such as epilepsy, autism, schizophrenia, and Alzheimer's disease. However, the mechanisms underlying HSP are poorly understood. At the *Drosophila* neuromuscular junction (NMJ), the cac^S mutation in the $Ca_v2.1$ voltage-gated Ca^{2+} channel leads to impaired HSP. Cac^S is a missense mutation that substitutes a phenylalanine with an isoleucine in a transmembrane segment 6 in domain III of $Ca_v2.1$, but whether this mutation alters $Ca_v2.1$ function is unknown. Here, we characterized the functional impact of this mutation in HEK293-T cells expressing wild-type (WT) or mutant (cac^S) human $Ca_v2.1$ channels. $Ca_v2.1$ undergoes prominent Ca^{2+}-dependent facilitation (CDF), a positive feedback mechanism that enhances Ca^{2+} entry and may contribute to short-term synaptic facilitation. Notably, CDF was reduced for $Ca_v2.1$ channels harboring the cac^S mutation compared to WT. In addition, the cac^S mutation slowed the deactivation of I_{Ca} and I_{Ba} tail currents and inhibited current density without causing a change in expression levels of the channel as measured by immunofluorescence. We propose that by decreasing CDF and current density, the cac^S mutation prevents activity-dependent Ca^{2+} signals that are needed to trigger HSP at the *Drosophila* NMJ and potentially at other synapses

Disclosures: **J. Thomas:** None. **J. Hagen:** None. **C. Frank:** None. **A. Lee:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

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Program #/Poster #: PSTR006.12/B27

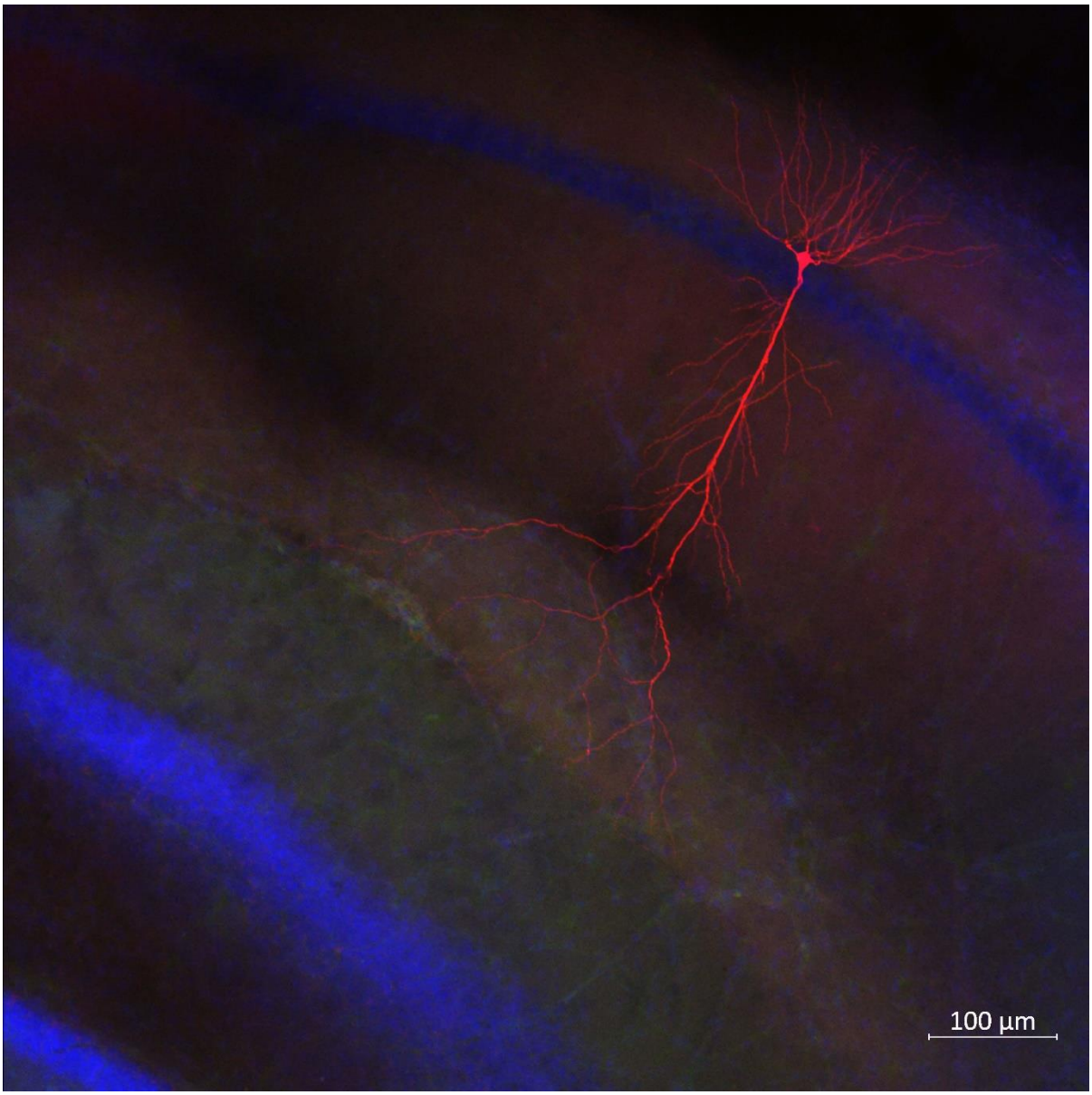
Topic: B.03. Ion Channels

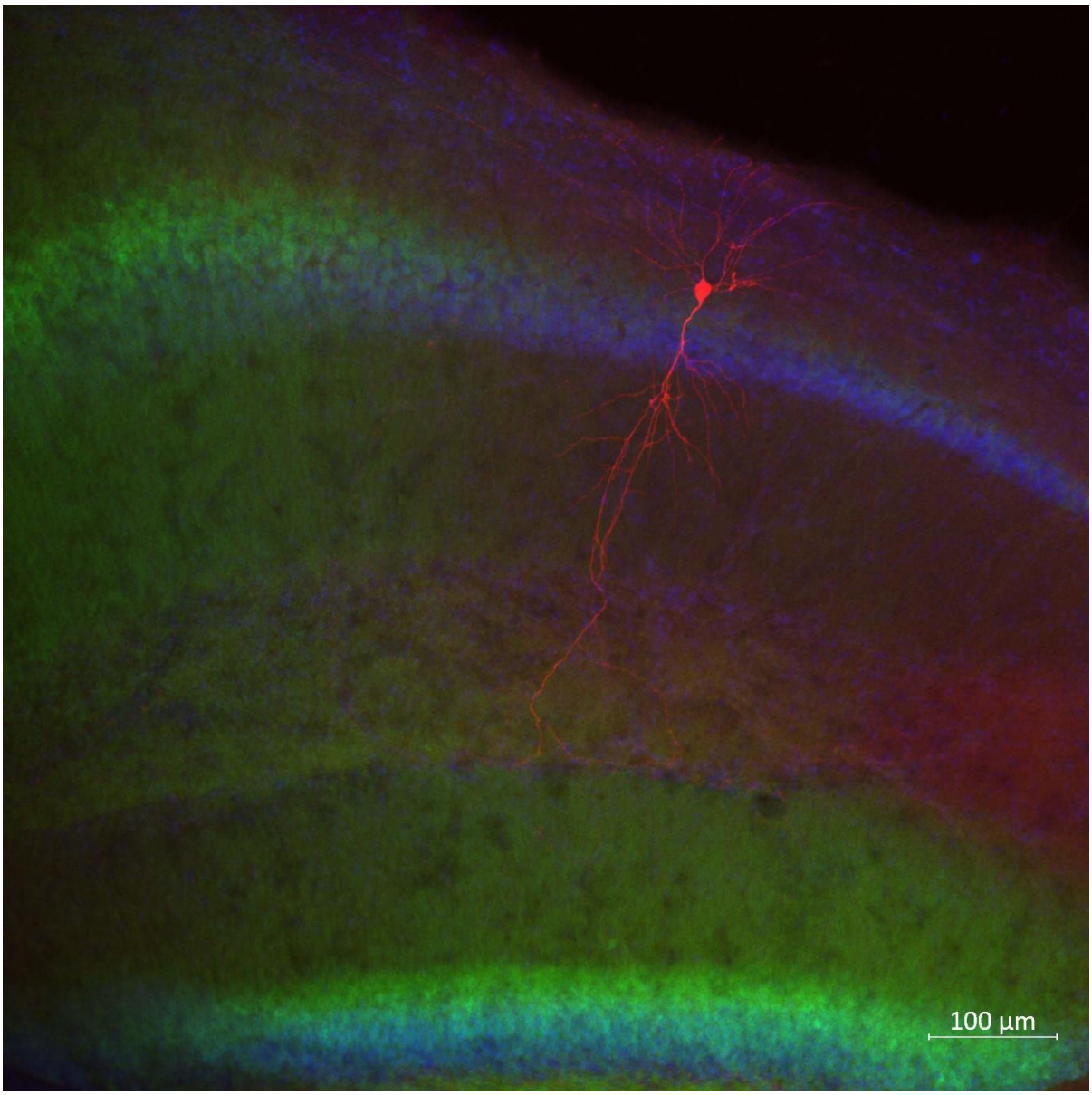
Support: NIH grant 1RO1MH115188-01 to YZ

Title: Inhibition of 14-3-3 proteins increases the intrinsic excitability of mouse hippocampal CA1 pyramidal neurons.

Authors: *V. VILMONT[1], J. B. LOGUE[2], Y. ZHOU[3], J. ZHANG[4], Y. WU[1];
[1]Florida State Univ., TALLAHASSEE, FL; [2]Col. of Med., Med. Univ. of South Carolina, Charleston, SC; [3]Col. of Med., Florida State Univ., Tallahassee, FL; [4]NIH/NCATS, Rockville, MD

Abstract: 14-3-3 proteins are a family of regulatory proteins that are abundantly expressed in the brain and enriched at the synapse. Mutation of these proteins have been linked to neurodevelopmental and neuropsychiatric disorders. Our group has previously shown that functional inhibition of these proteins by a dimeric 14-3-3 peptide inhibitor, difopein, in the mouse brain causes behavioral alterations and synaptic plasticity impairment in the hippocampus. In addition, we found an increased cFOS expression in difopein-expressing dorsal CA1 pyramidal neurons, indicating enhanced neuronal activity by 14-3-3 inhibition in these cells. In this study, we used slice electrophysiology to determine the effects of 14-3-3 inhibition on the intrinsic excitability of CA1 pyramidal neurons using a transgenic 14-3-3 functional knockout (FKO) mouse line. Our data demonstrate an increase in action potential firing frequency associated with 14-3-3 inhibition, as well as reveal action potential firing pattern shifts after novelty-induced hyperlocomotion in the 14-3-3 FKO mice. In addition, we examined difopein induced alteration in neuronal dendritic morphology and calcium channel current density. Together, these results provide novel information on the role 14-3-3 proteins play in regulating intrinsic and activity dependent neuronal excitability in the hippocampus.


100 µm



Disclosures: **V. Vilmont:** None. **J.B. Logue:** None. **Y. Zhou:** None. **J. Zhang:** None. **Y. Wu:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.13/B28

Topic: B.03. Ion Channels

Support: NIH Grant R01NS055251

Title: Cell-specific splicing of Cacna1a and Cacna1b genes is controlled by DNA binding proteins DNMT3a and TET1/2

Authors: *M. S. SISTI[1], A. SALAZAR[1], D. LIPSCOMBE[2];
[1]Dept. of Neurosci., [2]Carney Inst. for Brain Sci., Brown Univ., Providence, RI

Abstract: Cell-specific alternative splicing is a dynamic step in gene expression important for defining cell function. Our lab discovered a cell-specific splice site in Cacna1b, the gene that encodes CaV2.2, which modulates opioid action in heat-responsive sensory neurons. Ultralow methylation within alternatively spliced e37a, promotes CTCF binding, which in turn enhances exon inclusion in Cacna1b mRNA via cotranscriptional RNA splicing. E37a and e37b are mutually exclusive exons of identical size. E37a methylation state, and exon suppression/inclusion can be altered by modulating levels of the DNA methyltransferase DNMT3a or the ten-eleven translocases TET1/2 in vivo (Lopez-Soto et al., 2020). Cacna1b e37a is only expressed in a limited number of cell types, including in heat sensing nociceptors. The closely related Cacna1a gene (which encodes CaV2.1) contains homologous e37a and e37b spliced exons but e37aexpression is broader including cerebellar purkinje neurons and other neuronal subtypes in brain and DRG. Here we show that inclusion of e37a of Cacna1a is promoted by either inhibiting DNMT3a or overexpressing TET1/2 in vivo in N2a cell lines. Cacna1a e37a has been shown to enhance calcium-dependent facilitation and short-term synaptic depression in primary cortical neurons (Cingolani et al.,2023; Chaudhuri et al., 2004). To assess the function of e37a-containing CaV2.1 channels more globally, we generated two mouse strains which either expressed only Cacna1a-e37a (Cacna1ae37a-e37a*+/+) or only Cacna1a-e37b (Cacna1ae37b*-e37b+/+) by substituting in an imposter exon. Cacna1a-e37b only mice exhibit a tottering-like behavior and mice were viable for up to 4 weeks. In contrast, Cacna1a-e37a mice were not obviously different from WT in overall behavioral. In Cacna1a e37b, CaV2.1 protein levels were reduced substantially in cerebellum (30% of WT), and in Cacna1a-e37a, CaV2.1 levels were 40-50% of WT in cerebellum. RT-PCR using Cacna1a exon-specific primers showed the presence of Cacna1a e37a mRNAs in WT cerebellum. In Cacna1a-e37b only mice, the impostor exon e37b* (which replaced e37a) was found in all Cacna1a-e37b mRNAS. We are currently exploring the reason for the very different phenotypes of Cacna1a-e37b and Cacna1a-e37a only mice, given that both exhibit reduced protein expression in cerebellum. Specifically if the absence of e37a is the critical factor in explaining the profound loss of motor coordination in Cacna1a-e37b mice. Further experiments will explore exon-specific methylation states of wild type and exon substituted mouse lines.

Disclosures: M.S. Sisti: None. **A. Salazar:** None. **D. Lipscombe:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.14/B29

Topic: B.03. Ion Channels

Support: NIH Grant 1R35 GM141802
NIH Grant 5R01 HD097990

Title: Sex-specific alterations in T-type calcium current and inhibitory synaptic transmission contribute to long-lasting hyperexcitability of thalamocortical networks in vivo after neonatal exposure to general anesthesia in mice

Authors: *V. TADIC, V. JEVTOVIC-TODOROVIC, S. M. TODOROVIC;
Anesthesiol., Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: It is well established that the exposure to general anesthetics (GA) during the critical periods of brain development in rodents and non-human primates can cause a widespread neurodegeneration. However, lasting effects of an early exposure to GA to neuronal function is not well studied. Here, we focused on the thalamocortical (TC) network since it is well known that its rhythmic oscillations are important for normal sensory processing, cognitive functions and consciousness. Mice pups were exposed at postnatal day (PND) 7 to either GA with sevoflurane (treated group: 3% for the first 2h of exposure; 2.4% for the other 4h) or mock anesthesia (control group: regular air supplemented with 30% O_2 for 6 hours). Approximately at PND 65 - PND 80, the animals were implanted with cortical electroencephalogram (EEG) electrodes and recordings were obtained 15 minutes before and 45 minutes after the intraperitoneal (IP) application of gamma-butyrolactone (GBL) to induce a characteristic spike-wave discharge (SWD) pattern on EEG. We found that there was a significant increase in cumulative SWD duration of about 2-fold ($p<0.001$) in treated (n=15) vs. control (n=19) groups. Interestingly, the significant increase was only observed in female animals. In ensuing voltage-clamp recordings, we studied properties of T-type calcium currents (T-currents) of VB neurons (n=15 control; n=25 treatment). We found increased peak T-current densities in the GA group (about 40%) and depolarizing shift of about 3mV in mid-point of activation ($p<0.05$) when compared to the control group. Synaptic plasticity of the VB neurons was next evaluated by the voltage-clamp recordings of spontaneous inhibitory postsynaptic currents (sIPSCs). We found that sIPSCs in the GA group (n=18) were about 70% more frequent ($p<0.005$) compared to the control group (n=11) and had higher average event amplitudes for about 65% compared to the control group ($p<0.0005$). We next performed qPCR analyses of Slc32a1 which encodes vesicular GABA transporter (VGAT). Indeed, we found that expression of Slc32a1 was about 65% increased only in the female animals exposed to the GA in the neonatal period (n=8) compared to the control female group (n=7). We conclude that mice exposed to GA during early life exhibit chronic hyperexcitability in TC networks. In GA-treated group, VB thalamic neurons showed stronger inhibitory input due to upregulated VGAT, which could recruit more T-type channels. We posit that ongoing increased inhibitory input, altered biophysical properties and higher T-current densities in VB neurons may work in concert to produce hyperexcitable state observed in our *in vivo* EEG recordings in GA group.

Disclosures: V. Tadic: None. **V. Jevtovic-Todorovic:** None. **S.M. Todorovic:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.15/B30

Topic: B.03. Ion Channels

Support: The Shaughnessy Medical Fund
CVRI, Loyola Stritch School of Medicine
CHARM Institute, Loyola Stritch School of Medicine

Title: Treatment of aggressive meningioma cells with mibefradil leads to up-regulation of L-type channels supporting neoplastic progression

Authors: E. WHITE[1], V. C. PRABHU[2], J. THAKKAR[3], *E. S. PIEDRAS-RENTERIA[4]; [1]Cell and Mol. Physiol., Loyola Univ., Maywood, IL; [2]Neurosurg. and Radiation Oncology, [3]Neurol., Loyola Med. Ctr., Maywood, IL; [4]Cell & Mol. Physiol., Loyola Univ. Chicago, Maywood, IL

Abstract: Meningioma categorized as WHO grade III are rare but highly aggressive primary intracranial neoplasms with high recurrence rates following surgical resection and radiation treatment and an overall poor prognosis. Medical therapies for WHO grade III meningiomas are limited; avastin, everolimus, mifepristone, octreotide, and hydroxyurea (HU) are currently used off-label to treat unresectable progressive or recurrent WHO grade III meningiomas. We have previously demonstrated the presence of voltage-gated calcium channels (VGCC) $Ca_V1.2$, 1.3, 2.1, 2.2, 3.1, 3.2, and 3.3 in MN cells *in vitro*. Moreover, blockade of T-type VGCCs with clinically relevant concentrations of mibefradil (MIB) or nimodipine (NIMO) decreases cell viability and proliferation to a similar degree as HU, demonstrating their importance. Combination treatment (CT) using MIB with HU resulted in an enhancement of HU's effect after 2-day treatment; this effect was not observed with CT of NIMO and HU, suggesting L-type channels target a redundant cell cycle pathway (S phase) already effectively blocked by HU, in contrast to MIB's known effects on apoptosis and cell cycle arrest at the G_1/S checkpoint. In this study we further uncover changes in MN response after treatment with MIB over 7 days, resulting in a loss of efficacy, suggesting compensatory changes in calcium channel expression in MN. Triple combination with HU, MIB, and NIMO, or sequential treatment with HU+MIB followed by HU+NIMO restored the enhancement effect, further decreasing cell viability compared to HU monotherapy, corroborating that L-type channels are upregulated, compensating for the decrease of functional T-type channels. Interlaced treatment displayed less efficacy than CT overall. The use of FDA-approved VGCC antagonists in combination with HU could be a promising avenue for the treatment of malignant MN.

Disclosures: E. White: None. **V.C. Prabhu:** None. **J. Thakkar:** None. **E.S. Piedras-Renteria:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.16/B31

Topic: B.03. Ion Channels

Support: NIH Grant 1R15GM148923-01

Title: Synergy Between RNA Editing and Alternative Splicing Modulates the Biophysical and Pharmacological Properties of the Voltage-Gated Calcium Channel CaV1.3

Authors: *M. RUGGIU[1], W. MUNYAO[2], Z. WANG[1], C. BEAUVIL[1], Y. YU[1];
[1]Biol. Sci., St. John's Univ., Queens, NY; [2]St. John's Univ., Queens, NY

Abstract: Alternative splicing and adenosine-to-inosine RNA editing are post-transcriptional processes that promote proteomic diversity in the brain. Their dysregulation is linked to neurological and neurodegenerative diseases including amyotrophic lateral sclerosis, epilepsy, depression, and schizophrenia. Voltage-gated calcium channels (VGCCs) are crucial for neurotransmitter release, hormone secretion, and muscle contraction. The L-type VGCC CaV1.3 is critical for auditory signaling, cardiac pacemaking, neuronal firing, and hormonal secretion. Its negative activation voltage range enables it to open at hyperpolarized membrane potentials, a feature critical for its physiological role in neuronal rhythmic pacemaking and synaptic plasticity. Mutations in CACNA1D, the CaV1.3-encoding gene, cause seizures, neurologic abnormalities, and deafness. CaV1.3 is the only VGCC undergoing RNA editing, with edited variants present in the CNS but absent elsewhere. Unedited channels allow greater calcium influx, enhancing neuronal excitability and synaptic transmission, suggesting RNA editing negatively regulates these processes. Alternative splicing in the CaV1.3 C-terminus yields long and short variants with distinct gating and pharmacological properties. An alternative 3' splice site in exon 43 produces a CNS-specific, shorter CaV1.3 43S variant lacking the distal C-terminal auto-modulatory domain (DCRD) but retaining the proximal one (PCRD). The full-length variant contains a functional CTM composed of PCRD and DCRD, modulating channel function by regulating calmodulin function. CaV1.3 43S exhibits short gating properties with a more negative current window and higher open probabilities. Despite the discovery of RNA-edited CaV1.3 43S variants in the brain, which splice variants are edited is largely unknown, and the relationship between CaV1.3 alternative splicing and RNA editing is largely unexplored. We discovered an unexpected synergy between RNA editing and alternative splicing where splicing at exon 43, giving rise to CaV1.3 43S, results in a 3-fold increase in RNA editing at the IQ domain. Our data suggest that RNA editing is a loss-of-function mechanism that greatly decreases calcium influx and shifts activation threshold and current window to more depolarized potentials. By increasing the threshold for activation and decreasing availability at subthreshold potentials, RNA editing could serve as a mechanism preventing calcium overload in neuronal cells, safeguarding neurological integrity, and highlighting the intricate interplay between different RNA processing mechanisms in neuronal physiology and pathology.

Disclosures: **M. Ruggiu:** None. **W. Munyao:** None. **Z. Wang:** None. **C. Beauvil:** None. **Y. Yu:** None.

Poster

PSTR006: Voltage-Gated Calcium Channels

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.17/B32

Topic: B.08. Epilepsy

Title: Alterations to the structure-function relationship of Calcium Binding Protein 4 caused by the G155D point mutation associated with Autosomal Dominant Nocturnal Frontal Lobe Epilepsy.

Authors: *V. S. MORRIS[1], D. RIGDEN[2], C. DART[1], N. HELASSA[1];
[1]Biochemistry, Cell and Systems Biol., Univ. of Liverpool, Liverpool, United Kingdom;
[2]Biochemistry, Systems and Cell Biol., Univ. of Liverpool, Liverpool, United Kingdom

Abstract: Autosomal Dominant Frontal Lobe Epilepsy (ANDFLE) is a partial epilepsy characterised by frequent focal seizures often with vocalisation, aura and assumption of posture. Onset usually occurs within the first 20 years of life and 30% of patients are resistant to treatment. Calcium Binding Protein 4 (CaBP4) modulates the activity of voltage-dependent calcium channels including Cav1.3 and Cav1.4. Cav1.4 is key for maximal glutamate release from the ribbon synapses of rod photoreceptors in low light conditions. The G155D point mutation in CaBP4 has been previously associated with ADNFLE, however its effect on the structure-function relationship of CaBP4 is still unknown. Using computational biology tools (AlphaFold and DynaMut), we revealed that the G155D mutant has a higher number of intra-molecular interactions and increased flexibility. Circular Dichroism (CD) showed a significant decrease of 10 % in alpha-helical content and a 5 % increase in unordered structure in calcium-bound (n=5) and calcium-free conditions (n=5). DynaMut also predicted a reduction in protein stability for the G155D mutant. Using SGS-PAGE and densitometry analysis, we showed that G155D was more susceptible to protease digestion, with V50 values in calcium-free conditions decreasing from 0.54 ± 0.01 υg/ml (n=6) to 0.37 ± 0.01 υg/ml (n=5) and from 1.10 ± 0.05 υg/ml (n=7) to 0.81 ± 0.05 υg/ml (n=7) in calcium-bound conditions. Using CD, we showed that the G155D mutation causes a significant decrease in thermostability with V50 values decreasing from 44.0 ± 0.8 °C to 37.9 ± 0.5 °C in calcium-free conditions (n=6) and from 82.5 ± 1.3 °C to 76.2 ± 1.2 °C when calcium-bound (n=6). Intrinsic fluorescence spectroscopy (Tyrosine) showed a 2-fold reduction in Ca2+ affinity for the G155D variant (n=3), when compared to wild-type. CaBP4's binding affinity for the IQ domains of voltage-dependent calcium channels (Cav1.3, Cav1.4) was assessed via isothermal titration calorimetry and showed that the G155D mutant caused a reduction in the binding affinity to both domains. For both Cav1.3 and Cav1.4 IQ domains a 4.7-fold reduction in affinity was observed from K_d CaBP4 = 1.85 ± 0.2 uM (n=5) to K_d G155D = 8.67 ± 0.4 υM (n=7) and from K_d CaBP4 = 1.59 ± 0.2 uM (n=5) to K_d G155D = 7.41 ± 0.5 υM (n=6) respectively. Our findings demonstrate that the G155D mutation significantly impacts the structure, stability and function of CaBP4. This study contributes to our understanding of the mechanism in which the CaBP4 G155D point mutation leads to ADNFLE and could pave the way for the design of novel, more efficient therapies.

Disclosures: **V.S. Morris:** None. **D. Rigden:** None. **C. Dart:** None. **N. Helassa:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.01/B33

Topic: B.05. Synaptic Plasticity

Support: CIHR Project Grant 178281
The Scottish Rite Charitable Foundation of Canada Award

Title: Endocannabinoid-mediated short-term plasticity is heterogenous across the mouse cerebellum

Authors: *F. MUDLAFF[1,2,3], W. T. FARMER[4], A. SUVRATHAN[5,2,3];
[1]Integrated Program in Neurosci., McGill Univ., Montreal, QC, Canada; [2]Centre for Research in Neuroscience, Montreal, QC, Canada; [3]BRaIN Program Research Institute of the McGill University Health Center, Montreal, QC, Canada; [4]Dept. of Pharmacol. and Neurosci. Ctr., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [5]Neurol. and Neurosurg., Pediatrics, McGill Univ., Montreal, QC, Canada

Abstract: The cerebellum is characterized by a uniform cytoarchitecture while displaying a region-specific functional diversity ranging from motor to cognitive function. To date, it remains unclear how the cerebellum can execute these diverse functions. Learning requires rapid and lasting synaptic changes which are mediated through short- and long-term forms of plasticity. Previous studies have indicated a heterogeneity in long-term plasticity across functional distinct lobules of the cerebellum, however, whether short-term plasticity (STP) displays a similar heterogeneity remains unknown. STP at parallel fiber to Purkinje cell synapses is mediated by endocannabinoid retrograde signaling resulting in a reduction in neurotransmitter release probability upon binding to presynaptic cannabinoid receptor 1 (CB1R). Throughout development, CB1R expression undergoes drastic changes and is believed to display a sexual dimorphism in forebrain areas, however, little is known about the cerebellum. In the mouse cerebellum, CB1R has been demonstrated to be more abundant in anterior compared to posterior lobules, which are associated with distinct functions; whether these different expression patterns affect STP has not been investigated yet. To bridge the gap in our current understanding, we assessed endocannabinoid-mediated STP at parallel fiber to Purkinje cell synapses in functionally distinct lobules. We combined whole-cell recordings of Purkinje cells from acute cerebellar slices of wildtype mice of both sexes with biochemical analysis of key players of the endocannabinoid signaling pathway. Whole-cell recordings suggest a sexual dimorphism in the probability of inducing STP during early adolescence (female n = 6, male n = 3). Furthermore, in female mice (n = 6) we observed a disparity in the strength of plasticity across anterior and posterior lobules. Lastly, our data indicated differences in the induction probability of STP

between synapses located on the ascending granule cell axon and parallel fibers (ascending synapses, n = 16; parallel fiber synapses, n = 15), which are believed to have different physiological properties. Taken together, our data suggests a heterogeneity in endocannabinoid plasticity across functionally distinct lobules of the anterior and posterior cerebellum and across granule cell axonal and dendritic synapses. Together, our data provides evidence of a previously unelaborated synaptic and regional heterogeneity of endocannabinoid mediated STP in the cerebellum. These findings are particularly relevant for improving the design of endocannabinoid-based treatment strategies for a range of neurodevelopmental diseases.

Disclosures: F. Mudlaff: None. **W.T. Farmer:** None. **A. Suvrathan:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.02/B34

Topic: B.05. Synaptic Plasticity

Support: NIH Grant 5R01MH130428-02

Title: Mechanisms of presynaptic short-term plasticity in the CA3 microcircuit

Authors: *M. BARRAZA, J. N. ARMSTRONG, A. CONTRACTOR;
Neurosci., Northwestern Univ., Chicago, IL

Abstract: Mechanisms of presynaptic short-term plasticity in the CA3 microcircuit
Barraza, M.[1], Armstrong, J.N.[1], and Contractor, A.[1,2,3]
[1]Department of Neuroscience, Feinberg School of Medicine, Northwestern University, Chicago IL 60611.[2]Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University Chicago IL 60611.[3]Department of Neurobiology, Weinberg School of Arts and Sciences, Northwestern University, Evanston IL 60201.
Disclosures: None
Key Words: Mossy fiber synapse, facilitation, synaptotagmin 7
Mossy fiber (MF) synapses are formed by the axons of dentate granule cells with their downstream targets providing the flow of information into the CA3 region of the hippocampus. MF axons make synapses with both pyramidal cells (PCs) and *stratum lucidum* interneurons (SLINs) in the CA3, producing a direct excitation of PCs and feedforward inhibition through SLINs onto the local network. The properties of these two synaptic connections have divergent properties with MF-PC synapses showing strong facilitation and the MF-SLIN synapses mostly depressing during a burst of presynaptic granule cell activity. This results in a net effect of reduced inhibition and increased excitation during bursts of high frequency presynaptic firing that causes suprathreshold activation of CA3 PCs and thus acts as a high pass filter. Despite a large body of research on these synaptic mechanisms, it is not clear what underlies this divergent

synaptic behavior of synapses formed by the same axon and, in some cases, by different compartments of the same presynaptic terminal. We tested whether the high affinity Ca^{2+} sensor synaptotagmin 7 (Syt7) is responsible for creating this high pass filter in the CA3 microcircuit. Utilizing a newly created conditional knockout (cKO) mouse line where Syt7 is ablated in the dentate granule cells, we performed voltage clamp recordings of excitatory postsynaptic currents (EPSCs) and measured short term plasticity of MF connections onto both PCs and SLINs. Comparing these synapses during trains of stimulation in the range of normal granule cell firing provided insight into how presynaptic Syt7 affects synaptic properties. Moreover, using minimal extracellular stimulation and current clamp recording from CA3 PCs we analyzed MF excitatory postsynaptic potential (EPSP)-spike coupling in cKO mice to determine how altered presynaptic dynamics affected the detonator properties of MF synapses. Identifying the presynaptic mechanisms responsible for information transfer will allow future work to directly test the molecular processes underlying complex hippocampal-dependent behaviors.

Disclosures: **M. Barraza:** None. **J.N. Armstrong:** None. **A. Contractor:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.03/B35

Topic: B.05. Synaptic Plasticity

Support: KAKENHI no. JP23H05476 from JSPS

Title: Astrocytic Modulation of Cell Assembly Formation with STP-dependent STDP

Authors: *R. KOSHKIN[1], T. FUKAI[2];
[1]Okinawa Inst. of Sci. and Technol., Tancha, Japan; [2]Okinawa Inst. of Sci. and Technol., Onna-son, Japan

Abstract: Cell assemblies, conceptualized as graph-like structures within neuronal networks, serve as fundamental units for memory representation. While the importance of long-term potentiation (LTP) in forming these structures is well established, the role and contribution of other factors like astrocytes and short-term plasticity (STP) remain underexplored. This study probes the formation and dynamic reorganization of cell assemblies in a hippocampal CA3 model (spiking recurrent neural network) evolving under an STP-dependent symmetric spike-timing-dependent plasticity (STDP). We introduced two enhancements in our learning rule: (1) synaptic changes at excitatory synapses are influenced by the available quantity of neurotransmitter (Froemke et al., J Neurophysiol 2006), shown to support sequence learning via reverse replay (Haga & Fukai, eLife 2018), and (2) we incorporated the impact of astrocytes by varying neurotransmitter release probabilities, reflecting recent findings on the role of astrocytic NMDA receptors in synaptic variability (Chipman et al., eLife 2021). Our simulations

demonstrate that both STP-dependent and independent symmetric STDP facilitates robust cell assembly formation without structured input. However, STP-dependent STDP uniquely promotes stability in cell assembly structure and responsiveness to external stimuli, traits advantageous for memory adaptability. Notably, astrocytes enhance the self-organization and responsive reorganization of these assemblies under the STP-dependent STDP rule. Our findings underscore the possible computational benefits of STP-dependent symmetric STDP and propose an expanded regulatory function of astrocytes in neural plasticity and memory formation.

Disclosures: R. Koshkin: None. **T. Fukai:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.04/B36

Topic: B.05. Synaptic Plasticity

Support: Grant from the Inspire Foundation
Grant from the Injured Players' Foundation of the Rugby Football Union

Title: Movement Paired with Nerve Stimulation Generates Plasticity in the Human Motor System

Authors: *L. A. CLEMENTS, O. A. BURTON, N. NORMAN, S. N. BAKER;
Newcastle Univ., Newcastle Upon Tyne, United Kingdom

Abstract: This project investigated a novel mechanism of generating plasticity in the human motor system. Healthy human subjects produced 200 index finger abduction movements, in groups of 4, in time to a metronome. On the 4th and final beat of each group of abductions, the ulnar nerve was stimulated. Motor evoked potentials (MEPs) in response to transcranial magnetic stimulation (TMS) over the primary motor cortex were recorded before and after the pairing. MEPs were similarly enhanced when the ulnar nerve stimulation occurred just before or just after the burst of EMG activity in the first dorsal interosseous muscle associated with the repetitive movements. This indicated that pairing did not require precise relative timing to induce plasticity. Ulnar nerve stimulation alone had no effect on MEPs, whilst performing repetitive movements alone generated a small but significant increase in MEPs. This highlights the importance of pairing movement with nerve stimulation to generate maximal plastic change. Further studies investigated the level at which plasticity might occur. MEPs were measured following electrical stimulation at the cervico-medullary junction (cMEPs); a method thought to activate corticospinal axons distant to the cell body, thus unaffected by changes in cortical excitability. cMEPs remained unchanged before and after pairing repetitive movement with ulnar nerve stimuli, suggesting that plastic changes do not occur at the spinal level. The StartReact effect measures the decrease in reaction time when a cue is paired with a loud (startling) sound,

shown to measure reticulospinal contributions to movement. Measures of StartReact did not increase after vs before pairing repetitive movement with ulnar nerve stimuli. This suggests that plastic changes do not occur in the reticulospinal system. Pairing repetitive movements with nerve stimuli is a promising approach to enhance motor output by generating plasticity seemingly at the cortical level. This novel protocol shows potential applications for improving motor deficits following damage, resulting from conditions such as stroke or spinal cord injury.

Disclosures: L.A. Clements: None. **O.A. Burton:** None. **N. Norman:** None. **S.N. Baker:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.05/B37

Topic: B.05. Synaptic Plasticity

Support: Fonds de Recherche du Quebec
Canadian Institutes of Health Research Grant 11365

Title: The involvement of neocortical astrocytes in timing-dependent long-term depression

Authors: *A. WATANABE[1], C. GUO[1], P. J. SJOSTROM[2];
[1]McGill Univ., Montreal, QC, Canada; [2]Dept of Med., McGill Univ., Montreal, QC, Canada

Abstract: Spike-timing dependent plasticity - where the millisecond temporal order of spiking in connected neurons determines whether their synapses strengthen or weaken - is a biologically plausible experimental paradigm of cellular learning, for which the role of astrocytes is just starting to be elucidated.
To probe astrocyte involvement in timing-dependent long-term depression (tLTD), we used sodium fluoroacetate (NaFAC; 5 mM), a metabolic inhibitor of glia. P11 - P16 C57BL/6J mouse acute visual cortex slices were pre-incubated in NaFAC prior to performing quadruple patch clamp on layer-5 pyramidal cells. In monosynaptically connected pairs, tLTD was induced by 20-Hz spike pairings with 25 ms post-before-pre ordering. Compared to no-induction controls with and without NaFAC (after/before = 101% ± 3%, n = 14), after tLTD induction, unitary EPSPs depressed without (74% ± 6%, n = 7, $p < 0.01$) but not with NaFAC pre-incubation (103% ± 7%, n = 7, $p = 0.76$; all t-tests after ANOVA, $p < 0.01$).
Previously, we found that astrocyte spontaneous Ca^{2+} events mature with development. Over the ages P7 to P50 (n = 36 astrocytes), using the calcium indicator Fluo-5F (200 µM), intracellular Ca^{2+} signals within astrocytes became shorter (rho = -0.54, $p < 0.001$), more frequent (rho = 0.63, $p < 0.001$), and more decorrelated (rho = -0.54, $p < 0.01$). We observed that these properties stabilized after ~P15. Therefore, we carried out subsequent astrocyte Ca^{2+} imaging studies on or after P15.

We expressed the opto-α1AR opsin, a light-sensitive Gq-protein-coupled receptor, by performing neonatal injections of an adeno-associated virus (AAV1-GfaABC1D::OptoGq-eYFP) into the visual cortex of C57BL/6J mice . Here, we paired our previous tLTD induction protocol with blue light stimulation (445 nm, 45 ms pulse duration at 20 Hz) to activate the opsin during the induction period. In preliminary experiments, this manipulation resulted in no tLTD after induction.
A working model of tLTD involves retrograde endocannabinoid signalling. Astrocytes are known to possess endocannabinoid receptors. We found that bath application of ACEA (125 nM), an endocannabinoid receptor agonist, increased the frequency of astrocyte Ca2+ transients (72 ± 21% ACEA, n = 64 ROIs vs 13 ± 17% control, n = 42 ROIs, $p < 0.05$).
Overall, our findings suggest a critical role for astrocytes in cortical tLTD.

Disclosures: **A. Watanabe:** None. **C. Guo:** None. **P.J. Sjostrom:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.06/B38

Topic: B.05. Synaptic Plasticity

Support: NS 127219

Title: Imaging voltage changes to study short term plasticity of excitatory synapses on genetically targeted parvalbumin interneurons and mossy cells in the dentate gyrus

Authors: *S. SENGUPTA, M. B. JACKSON;
Dept. of Neurosci. and Neurosci. Training Program, Univ. of Wisconsin-Madison, Madison, WI

Abstract: The dentate gyrus gates the entry of information into the hippocampus. A variety of excitatory and inhibitory cell types process this information, and plasticity in these synapses can alter this processing. Classically, patch clamp and field potential recordings are used to assess short-term plasticity. However, these methods lack specificity. Here, in an exploratory investigation we targeted a genetically encoded hybrid voltage sensor (hVOS) to study the responses of mossy cells and parvalbumin (PV) interneurons and used voltage imaging in the different layers of the dentate gyrus to characterize short term synaptic plasticity with sequential paired-pulse stimulation of different excitatory inputs. The hVOS probe targets to the inner leaflet of the plasma membrane, and in the presence of dipicrylamine generates a fluorescence signal upon membrane depolarization. Cre drivers targeted the probe to the mossy cells (*Calcrl*) and PV interneurons (*Pvalb*), and optical recordings were performed in 300 µm coronal and horizontal slices. Stimulation was applied to the granule cell layer, the CA3 region, and the perforant path, and paired pulses spaced at 20 - 50 ms were used to test short-term plasticity. Peak amplitude (ΔF/F) was analyzed in mossy cells and PV interneurons in the hilus, inner

molecular layer, and granule cell layer. Responses of the PV interneurons to granule cell layer stimulation depressed to similar degrees in the hilus (0.74 ± 0.42) and molecular layers (0.80 ± 0.35, p >0.05, 8 slices; 4 animals) on applying stimuli spaced 40 and 50 ms apart. However, on applying stimuli spaced 20 ms apart, summation was evident to similar degrees in the hilus (1.27±0.60) and molecular layer (1.31±0.43, p>0.05, 10 slices; 5 animals). In contrast, mossy cells showed variable paired-pulse plasticity across different slices (n=8, 4 animals). In some slices, plasticity varied between mossy cell populations. In conclusion, imaging voltage changes using hVOS is a versatile method to study short term plasticity of excitatory synapses in the dentate gyrus.

Disclosures: S. Sengupta: None. **M.B. Jackson:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.07/B39

Topic: B.05. Synaptic Plasticity

Support: Burroughs Wellcome Fund's Career Award at the Scientific Interface

Title: Unraveling the ability of of inhibitory subtypes to modulate noise correlations

Authors: *J. N. NELSON[1], G. HANDY[2];
[1]Biomed. Engin., Univ. of Minnesota, Twin Cities, Minneapolis, MN; [2]Mathematics, Univ. of Minnesota, Minneapolis, MN

Abstract: Recent theoretical neuroscience research has made significant strides, moving beyond the conventional excitatory-inhibitory framework to incorporate the diverse array of inhibitory subtypes present in neural networks. Contrary to the traditional view of inhibitory neurons as a single class, it has been revealed that 80% of interneurons exist in three distinct subtypes: parvalbumin (PV)-, somatostatin (SST)-, and vasointestinal peptide (VIP)-expressing neurons, each exhibiting unique characteristics. Moreover, the differences in how these subtypes are integrated into the cortical circuitry are not trivial.
For instance, while excitatory (E) neurons project onto all three subtypes, the connection from E to SST neurons is significantly facilitated, whereas the connection to PV neurons is depressed. VIP neurons, on the other hand, predominantly project onto SST neurons. Additionally, PV neurons stand out as the only subtype receiving all the same inputs as E neurons. Understanding these intricate patterns of connectivity and short-term plasticity is essential to deciphering the distinct roles played by each subtype in shaping network dynamics within the mouse primary visual cortex. In our study, we delve deeper into this network architecture and investigate how the unique connectivity and plasticity rules of these inhibitory subtypes contribute to establishing network dynamics. To achieve this, we expand a network model of exponential integrate-and-fire

neurons, incorporating plasticity variables as described in the seminal work by Tsodyks et al. (1998). Our simulations demonstrate how these distinct features of connectivity and plasticity are critical in regulating noise correlations within the excitatory population, often leading to novel and unexpected outcomes. Furthermore, by simulating inputs that mimic those received during locomotion, we shed light on how this regulatory mechanism changes across different brain states. Our findings not only provide valuable insights into the functional roles of inhibitory subtypes but also highlight the complexity and adaptability of cortical networks in response to varying environmental inputs.

Disclosures: **J.N. Nelson:** None. **G. Handy:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.08/B40

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R00 MH118423-05

Title: Plasticity in feedback inhibition affects CA1 assembly membership

Authors: ***G. YANG**[1], Z. SACCOMANO[2], P. PAUDEL[3], S. A. MCKENZIE[4];
[1]Univ. of New Mexico Dept. of Neurosciences, Albuquerque, NM; [2]Neurosci., City Univ. of New York, Brooklyn, NY; [3]Neurobio. and Behavior, Cornell Univ., Ithaca, NY; [4]Neurosciences, UNM HSC, Albuquerque, NM

Abstract: Memory is believed to be stored in the pattern of synaptic connectivity between neurons. Coincident neural activity between connected cells in the hippocampus is known to change synaptic strength, but the rules for how activity affects connectivity *in vivo* are largely unknown. Novel experiences show additional neuromodulation that could gate plasticity as well. Excitatory neurons in the CA1 subregion of the hippocampus primarily influence each other indirectly through inhibitory interneurons. Therefore, we tested the plasticity rules governing the excitatory synaptic strength onto local inhibitory cells. The red-shifted opsin ChrimsonR was expressed under the parvalbumin (PV) promoter to target fast-spiking interneurons (PV+ INT), and blue-shifted Channelrhodopsin 2 (Chr2) was expressed under the calcium/calmodulin-dependent protein kinase type II alpha (CaMKIIα) promoter to target primarily pyramidal cells (PYR) in CA1. Theta burst stimulation (TBS) was used to induce plasticity using red (635 nm) and blue (473 nm) light pulsed at 8 Hz either simultaneously to pair PYR and PV+ INT activity, or asynchronously to uncouple PYR and PV+ INT in the home cage and in a novel context. Paired TBS increased PYR response to ChR2 stimulation and increased ripple recruitment. Unpaired TBS did not affect PYR responsiveness to ChR2 stimulation shown by decreased firing during spontaneous ripples. Experiments showed decorrelation in distinct PYR population firing

rate activity depending on synchronous or asynchronous pairing with PV+ INT. In a second experiment, mice exposed to a novel context during TBS pairing will test neuromodulation on synaptic strength. We expect plasticity induction in a novel environment will enhance the stimulation-related changes in neural excitability and assembly structure. Together, our findings show the potential plasticity at the excitatory to inhibitory synapse in area CA1 of the hippocampus in controlling neural excitability and assembly membership.

Disclosures: **G. Yang:** None. **Z. Saccomano:** None. **P. Paudel:** None. **S.A. McKenzie:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.09/B41

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01

Title: Pairing vagus nerve stimulation with swallowing to restore vocal fold function after recurrent laryngeal nerve injury

Authors: *M. VAHID[1], R. A. MORRISON[3], M. P. KILGARD[5], S. A. HAYS[4], A. SHEMBEL[2,1];
[1]Brain and Behavioral Sci., [2]The Univ. of Texas at Dallas, Richardson, TX; [3]Univ. of Texas At Dallas, Richardson, TX; [4]Bioengineering, Univ. of Texas At Dallas, Dallas, TX; [5]Behavioral and Brain Sci., Univ. of Texas, Dallas, Richardson, TX

Abstract: Title: Pairing vagus nerve stimulation with swallowing to restore vocal fold function afterrecurrent laryngeal nerve injury**Abstract:**Injuries to the recurrent laryngeal nerve (RLN) result in laryngeal motion impairments like vocalfold paralysis, which often lead to persistent voice and swallowing difficulties. The key issue isthat the vocal fold rarely recovers movement after transaction or injury, due to randomreconnection of peripheral nerve fibers that lead to coactivation of adductor and abductorlaryngeal muscles (e.g., synkinesis) as well as upstream somatotopic disorganization of centralneural pathways.Current surgical interventions focus on medializing the vocal folds to improve contact betweenthe paralyzed and functioning vocal fold but fail to restore active vocal fold motion essential forvocalization and airway protection. One solution is to reorganize upstream motor pathways inthe central nervous system to improve downstream restoration of laryngeal muscle functionafter RLN injury. Drawing inspiration from previous studies demonstrating the efficacy ofelectrical vagus nerve stimulation (VNS) in enhancing motor recovery in other peripheral nerveinjury models, we applied VNS in a rat model of RLN injury. VNS-paired motor rehabilitation isthought to improve motor function by strengthening appropriate neural connectivity throughupstream endogenous central plasticity while reducing mistargeted connections within thecentral nervous system.The overarching

objective of this study was to pair VNS with swallowing, which maximallyadducts the laryngeal muscles essential for airway protection, and determine the effects ofVNS-paired swallowing on laryngeal motor function recovery in a rat RLN injury model. Theanimals received either a VNS implant and RLN injury (Experimental Group) or RLN injury only(Control Group). All animals recovered for 6 weeks after RLN injury to allow sufficient time forsynkinetic reinnervation and somatotopic disorganization before starting either swallowingrehabilitation or VNS-paired swallowing rehabilitation. Functional assessments involvedlaryngoscopy to quantify vocal fold movement and recorded ultrasonic vocalizations tocharacterize acoustic changes in vocal intensity and tonality. Restoration of vocal fold motion inthe VNS-paired swallowing group but not in the swallowing-only group shows promise for VNSas a therapeutic intervention for RLN injury. The findings of this study hold significant potentialfor informing novel treatment strategies for patients grappling with RLN injury-inducedlaryngeal motor impairments like vocal fold paralysis.

Disclosures: M. Vahid: None. **R.A. Morrison:** None. **M.P. Kilgard:** None. **S.A. Hays:** None. **A. Shembel:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.10/B42

Topic: B.05. Synaptic Plasticity

Support: SFB 1286

Title: Molecular and cellular mechanisms underlying drug-associated memories

Authors: *P. R. HUGUET[1,2], O. M. SCHLUETER[3,1];
[1]Universitaetsmedizin Goettingen, Goettingen, Germany; [2]International Max Planck Research School, Goettingen, Germany; [3]Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Addicted brains develop exceedingly rigid and long-lasting memories that associate the drug of abuse with a context. Consequently, re-exposure to drug-associated contexts often lead to relapse even after prolonged periods of withdrawal. Nonetheless, the underlying cellular and molecular mechanisms of drug-associated memories remain poorly understood. Repetitive exposure to cocaine generates silent synapses, synapses with stable NMDA-receptors but lacking AMPA-receptors, in the adult nucleus accumbens *de novo,* thereby creating novel opportunities of synaptic connections (Huang et al., 2009). Following unsilencing by the incorporation of AMPA-receptors, silent synapses regulate key aspects of drug-associated behaviors (Lee et al., 2013; Wang et al., 2021; Panopoulou et al., 2022). We hypothesize that these newly generated silent synapses reorganize the neural networks that encode drug-associated memories to award them a rigid and long-lasting nature. While nucleus accumbens-based adaptations might

contribute to regulate motivation and action, additional brain regions are likely involved to encode drug-context associations and the exceedingly rigid and compulsive drug taking behaviors. Using patch-clamp electrophysiology with minimal stimulation, we found that cocaine induces silent synapses in the dorsal striatum, a region implicated in habitual learning; and in the hippocampus, a region involved in associative learning; but not in the medial prefrontal cortex, involved in action control. Moreover, spine imaging analysis allowed to discriminate between *de novo* generated synapses and unsilencing of mature synapses. At a molecular level, thrombospondins and their neuronal receptors α2δ-1 have been described to contribute to synaptogenesis (Koh et al., 2019; J. Wang et al., 2021). Unexpectedly, silent synapse generation by drugs of abuse and during developmental critical periods exhibited distinct features on the dependence of α2δ-1, indicating parallel pathways of silent synapse generation and specific potentially druggable targets for cocaine generated silent synapses. These findings suggest that cocaine employs unique molecular mechanisms to remodel the glutamatergic network, affecting specifically the striatum and the hippocampus. Further molecular characterization will allow to understand the drug-induced neural adaptations, which could provide therapeutical targets to disrupt drug-associations.

Disclosures: P.R. Huguet: None. **O.M. Schlueter:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.11/B43

Topic: B.05. Synaptic Plasticity

Support: HHMI
European Research Council Horizon 2020 - MolDynForSyn #945700

Title: Brain-wide measurements and modeling of synaptic protein turnover reveals localized plasticity with subcellular control during learning

Authors: *B. MOHAR[1], C. BERGMANN[2], T. TCHUMATCHENKO[2], K. SVOBODA[3], N. P. SPRUSTON[1];
[1]Janelia Res. Campus, Ashburn, VA; [2]Univ. of Bonn Med. Ctr., Bonn, Germany; [3]Allen Inst. for Neural Dynamics, Seattle, WA

Abstract: Synaptic plasticity underlies learning and memory by altering neuronal connections in response to experiences. However, the loci of learning-induced synaptic plasticity, and the degree to which plasticity is localized or distributed, remain largely unknown. We developed a new method (DELTA[1]) that allows mapping of brain-wide changes in synaptic protein turnover with single-synapse resolution by using bioavailable Janelia Fluor dyes and HaloTag knock-in mice. During associative learning, the turnover of the ionotropic glutamate receptor

GluA2, an indicator of synaptic plasticity, was enhanced in several brain regions, most markedly in the hippocampus. In the hippocampal area CA1, GluA2 stability was regulated in an input specific manner, with more turnover in regions containing input from CA3 compared to entorhinal cortex. For both GluA2 and PSD95 (an excitatory post-synaptic scaffold protein) turnover in the CA1 region we saw non-linear gradients of lifetime. Specifically, shorter lifetime close to the cell body layer, longer lifetimes further away, and a sharp transition at the most distal section. We modeled lifetime using a linear 2-compartmental (dendritic and synaptic compartments) model and were able to correctly predict the trend of lifetime gradients along the dendrites of CA1. That is, shorter measurement intervals lead to steeper lifetime slopes. These modeling results also highlight that dynamics should be considered when interpreting protein lifetime measurements along dendrites. Finally, we propose extensions of DELTA that would improve the temporal, spatial, and cell type specificity of the method.
[1] https://www.biorxiv.org/content/10.1101/2022.11.12.516226v3

Disclosures: B. Mohar: None. **C. Bergmann:** None. **T. Tchumatchenko:** None. **K. Svoboda:** None. **N.P. Spruston:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.12/B44

Topic: B.05. Synaptic Plasticity

Support: NIH Grant T34GM136497
NIH Grant T32GM144876-02
UMBC Startup Fund

Title: Identifying areas of convergence between dorsal and ventral hippocampal pathways in the nucleus accumbens

Authors: *S. VANCE[1], A. COPENHAVER[1], T. LEGATES[1,2];
[1]Biol. Sci., Univ. of Maryland, Baltimore County, Baltimore, MD; [2]Physiology, University of Maryland School of Medicine, Baltimore, MD

Abstract: Establishing learned associations between rewarding stimuli and the context under which those rewards are encountered is critical for survival. Input from the hippocampus, a brain region integral in learning and memory, to the nucleus accumbens (NAc), a key area regulating motivated behaviors, is important for establishing associations between rewarding stimuli and related contextual information. This connection consists of two independent pathways originating from the dorsal (dHipp) or ventral (vHipp) hippocampus, which have previously been considered functionally and anatomically distinct. Recent findings from our lab and others show overlap in dHipp and vHipp terminal fields in the NAc, leading us to reconsider this view and

raising new questions regarding the potential interactions between these two pathways in the NAc. We used optogenetics, electrophysiology, and an innovative transsynaptic labeling technique in mouse models to investigate the anatomical innervation and physiological relevance of these two independent inputs. Our labeling technique allowed us to visualize dHipp innervated neurons, vHipp innervated neurons, and dually innervated neurons in the NAc. Optogenetic manipulation during whole-cell electrophysiology recordings confirmed the presence of dual innervation of individual neurons in the NAcSh via the dHipp and vHipp pathways and revealed heterosynaptic interactions between the two pathways. Altogether, these results confirmed that the vHipp and dHipp dually innervate a subset of neurons in the NAc, suggesting integration of vHipp and dHipp information at the level of individual neurons. Further probing of the physiological and behavioral relevance of this finding will provide novel insight as to how single neurons can integrate spatial and contextual information and how it influences learning processes.

Disclosures: S. Vance: None. **A. Copenhaver:** None. **T. LeGates:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.13/B45

Topic: B.05. Synaptic Plasticity

Title: Characterizing the effect of vagus nerve stimulation parameters on cortical plasticity

Authors: *P. ZARE[1], C. NEIFERT[2], S. A. HAYS[3], M. P. KILGARD[4];
[1]Bioengineering, The Univ. of Texas at Dallas, Richardson, TX; [2]Bioengineering, Univ. of Texas at Dallas, Richardson, TX; [3]Bioengineering, Univ. of Texas At Dallas, Dallas, TX; [4]Behavioral and Brain Sci., Univ. of Texas, Dallas, Richardson, TX

Abstract: Title: Characterizing the effect of vagus nerve stimulation parameters on cortical plasticityKeywords: Vagus, Plasticity, Motor Cortex Authors: Pariya Zare[1], Connor Neifert[1], Seth A. Hays[1,2], Michael P. Kilgard[2,3]Affiliations: [1] Department of Bioengineering, Erik Jonsson School of Engineering and Computer Science, The University of Texas at Dallas, 800 West Campbell Road, Richardson, TX 75080-3021, USA[2] The University of Texas at Dallas, Texas Biomedical Device Center, 800 West Campbell Road, Richardson, TX 75080-3021, USA[3] Department of Neuroscience, School of Behavioral and Brain Sciences, The University of Texas at Dallas, 800 West Campbell Road, Richardson, TX 75080-3021, USAPairing vagus nerve stimulation (VNS) with motor rehabilitation has emerged as a promising approach to enhance recovery from neurological injuries. The mechanism underlying the efficacy of VNS lies in its ability to enhance cortical plasticity. While it has been demonstrated that the stimulation parameters influence the magnitude of VNS-dependent plasticity, this relationship is complex. Identifying parameters that maximize the degree of VNS-dependent plasticity holds promise to

optimize the efficacy of this approach. In this study, we aimed to comprehensively characterize the interaction between different VNS parameters to better understand the mechanisms driving VNS-dependent plasticity. To do so, rats underwent training on a simple behavioral task over five days, during which VNS at varying parameters was paired with jaw movement while the rats were chewing. During these sessions, rats received one of three VNS parameter sets: standard (moderate intensity of 0.8mA, low frequency 30 Hz, and 16 pulses), long (low intensity 0.5mA, low frequency 30Hz, and 60 pulses), or short (high intensity more than 1mA, high frequency more than 100Hz, and a few numbers of pulses pulses). The day after the final session of behavioral training, we used intracortical microstimulation (ICMS) to evaluate plasticity in motor cortex. This study will clarify the relationship between VNS parameters and the degree of cortical plasticity.

Disclosures: P. Zare: None. **C. Neifert:** None. **S.A. Hays:** None. **M.P. Kilgard:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.14/B46

Topic: B.05. Synaptic Plasticity

Support: NSERC RGPIN - 2020-06757

Title: Exploring the effects of cTMS versus rTMS on measures of neuroplasticity through intervention and assessment

Authors: *C. DRAPEAU[1], F. ADAMS[2], J. PARK[1], S. FOGLIA[1], K. RAMDEO[3], A. J. NELSON[4];
[2]Kinesiology, [1]McMaster Univ., Hamilton, ON, Canada; [3]McMaster Univ., Hamilton, ON, ; [4]Dept Kinesiol, McMaster Univ., Hamilton, ON, Canada

Abstract: Repetitive transcranial magnetic stimulation (rTMS) is a powerful tool for the induction of neuroplasticity, offering potential therapeutic benefits for psychiatric and motor conditions (León Ruiz et al., 2018). However, the neuromodulatory effects of rTMS is limited and variable as the pulse is restricted to sinusoidal and biphasic in shape (Ridding & Ziemann 2010). Controllable pulse parameter TMS (cTMS) has the potential to increase neuromodulation as it allows for the different pulse shapes and widths to be delivered at high frequencies. Specifically, monophasic cTMS pulses, delivered at 10 Hz, produced larger and more long-lasting changes in cortical excitability compared to traditional biphasic rTMS (Arai et al., 2007). This study aimed to compare the effects of 10 Hz monophasic cTMS versus 10 Hz biphasic rTMS versus 10 Hz sham rTMS pulses delivered over primary motor cortex on measures of cortical excitability and inhibition. A total of 30 right-handed participants, aged between 18-35, received either 10 Hz rTMS, cTMS, or sham stimulation on 3 separate sessions in a pseudo-

randomized order, separated by a minimum of one week. Dependent measures were obtained immediately before and 10 minutes following the cessation of stimulation. Dependent measures included cortical excitability as assessed using the amplitude of the motor-evoked potential (MEP) evoked at each of 110%, 130%, and 150% resting motor threshold. Short-interval intracortical inhibition (SICI) was obtained with conditioning stimulus set to 80% of active motor threshold and test stimulus set to the intensity that evoked at 1 mV MEP in abductor pollicis brevis muscle representation. Saliva samples were obtained for analysis of the val66Met polymorphism to understand the study outcome as it relates to the genetic predisposition for the brain-derived neurotrophic factor. Preliminary results indicate that the greatest increase in excitability occurred via cTMS, then by rTMS, followed by sham at the 110% RMT intensity only. SICI was not altered by any stimulation type. These data suggest cTMS is a powerful modulator of cortical excitability. Further results are pending the completed gene analysis.

Disclosures: C. Drapeau: None. **F. Adams:** None. **J. Park:** None. **S. Foglia:** None. **K. Ramdeo:** None. **A.J. Nelson:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.15/B47

Topic: B.05. Synaptic Plasticity

Support: 1R01NS116051
1R21AG086934

Title: Neuron-specific regulation of extracellular vesicle secretion and content by NSG family members NSG1 and NSG2.

Authors: *L. VEGA[1], S. J. WILSON[2], A. SERRANO RODRIGUEZ[3], J. P. WEICK[4];
[1]Neurosci., Univ. of New Mexico, Albuquerque, NM; [2]Neurosciences, UNM, Albuquerque, NM; [3]Dept. of Neurosciences, Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM; [4]Neurosciences, Univ. of New Mexico, Albuquerque, NM

Abstract: Members of the neuron-specific gene family (NSG1-3) are small adaptor proteins that regulate trafficking and processing of multiple proteins throughout the secretory and endosomal pathways, including AMPA receptors, GRIP1, Neuregulin-1 and Sortilin-1. Previous research showed the presence of NSG1 in intraluminal vesicles of multivesicular bodies as well as binding to L1CAM, a protein known to be present in extracellular vesicles (EVs). Further, Proximity-based proteomic analysis of all family members showed that NSG1-3 biotinylated a plethora of proteins present in EVs including CFL1, CLTC1, ENO1, GAP43, and FLOT1. Here we directly examined whether NSG1-3 had a potential role in transcellular signaling via secretion of EVs from neurons. We found both NSG1 and NSG2 proteins were present in

abundance in EVs isolated from human and mouse neurons, but not from other cell types including astrocytes. Surprisingly, NSG3 was not present in EVs from any cell type tested. Differential centrifugation and filtration of various types of EVs showed that NSGs are not present in apoptotic vesicles, and were contained in EVs smaller than 200nm, suggesting their enrichment in exosomes. Using primary cultures from knockout animals of individual and combinations of NSG1-2, we further determined whether both EV abundance and content were significantly regulated by NSG1-2. Interestingly, loss of NSG1 significantly reduced overall EV abundance, while NSG2 had a significant effect on RNA content. Further, we found robust changes in transcripts that were previously shown to be altered in EVs taken from models of Alzheimer's disease. Together, these data point to a significant role of NSG1 and NSG2 on the secretion and content of EVs, specifically derived from neurons, which may have implications for neuronal plasticity and degeneration.

Disclosures: L. Vega: None. **S.J. Wilson:** None. **A. Serrano Rodriguez:** None. **J.P. Weick:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.16/B48

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R15DA049260
NIH Grant R15DA038092
Institutional BYU MEG Award

Title: Ketogenic Diet impact on Long-Term Potentiation in the Dorsal CA1 Hippocampal Region and Memory Behavior in Young and Adult Rodents

Authors: *J. EDWARDS[1], J. WEIGHT[1], J. CHRISTENSEN[2], M. DEW[3], E. SAITO[4], A. C. EVERETT[5], E. BARTHOLOMEUSZ[1];
[2]Dept. of Neurosci., [3]Neurosci., [4]Cell Biol. and Physiol., [1]Brigham Young Univ., Provo, UT; [5]Brigham Young Univ., Lehi, UT

Abstract: The ketogenic diet (KD) originally gained notoriety for its treatment of epilepsy. In recent years, the diet resurged for weight loss, though its effects on the neurological system are not understood. We examined cognitive effects of the KD on behavior and synaptic plasticity, employing CA1 hippocampal long-term potentiation (LTP) as a measure in young (2-8 weeks) and adult (7 months) C57 mice. For each of these groups, two treatment methods were employed: 1) a 3-4 week high lipid diet to increase ketone bodies *in vivo*, 2) bathing hippocampal slices in a controlled amount of ketone beta-hydroxybutyrate (BHB)-enriched artificial cerebrospinal fluid (ACSF) to produce a higher concentration of ketones than was

produced in rodents *in vivo*. Rodents on the lipid diet only reach ~2mM levels of blood ketones, less than what can be attained in humans. To ensure scientific rigor researchers were blinded as to which treatment group they were analyzing. Experiments were conducted using field electrophysiology. In young animals, there were no statistically significant differences in LTP between animals on KD and animals on a control diet (n values and stats). Adult mice on the KD however demonstrated significantly increased LTP (181 ± 18%; n=10; $p<0.05$) compared to animals on the control diet. We identified in trials of slices from 2-8 week old mice, we did not observe a difference in LTP between slices exposed to 7.5 mM BHB and 2.5 mM glucose for >2 hours (n=13; $p>0.05$) compared to controls of 0 mM BHB and 11 mM glucose (n=15;$p>0.05$). There were no statistically significant differences in LTP between slices from young male and female mice that were exposed to BHB or control ACSF. We are currently in the process of finishing up and analyzing the experiments with adult mice exposed to the BHB enriched ACSF. Additionally, in experiments involving young and adult mice given 3-4 weeks of the KD, we preformed behavioral Morris water maze experiments, which involve training an animal to find a submerged platform to test spatial memory. There was no significant ($p>0.05$) difference in time to platform or time in correct quadrant comparing both young mice treated with the high-fat diet chow (n=11) compared to control chow (n=12). In a prior publication, we demonstrate significant difference in the novel object recognition between adult and young mice (Sait et al., 2022, Metabolites). Overall, our data suggests the KD could have significant impact on neurological function such as LTP and memory behavior in adult mice, but not young mice.

Disclosures: **J. Edwards:** None. **J. Weight:** None. **J. Christensen:** None. **M. Dew:** None. **E. Saito:** None. **A.C. Everett:** None. **E. Bartholomeusz:** None.

Poster

PSTR007: Synaptic Plasticity: Short-Term and Spike-Timing Dependent Plasticity and Others

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.17/B49

Topic: B.05. Synaptic Plasticity

Title: Morphological changes in motor cortices and their relationship with motor performance of rats exposed to an aerobic excercise regimen

Authors: *J. I. ALFARO-MORENO, E. G. GONZÁLEZ-PÉREZ, S. ALCAUTER, C. J. CARRANZA-AGUILAR;
Inst. de Neurobiología, UNAM, Queretaro, Mexico

Abstract: The motor cortex (MC) is a brain region that plays a crucial role in the generation and control of voluntary movements of the body. It's typically divided into 2 regions: primary motor cortex (M1) and secondary motor cortex (M2). M1 is mainly involved in the execution of voluntary movements (Múnera, A., Troncoso, J., & García, J. M. D. 2005), while M2 is responsible for more complex functions related to motor planning and coordination (Cabrera, R.

S., & Romero, L. Z. 2022). These cortices are influenced by many environmental factors, one of them is aerobic exercise (Pietrelli, A. 2018). This influence can be observed at different levels, i.e. synaptic plasticity. One type of protein that allows us to understand this mechanism is the synaptophysin, which is found in the synaptic vesicles (Garcia, P. C., et al, 2012). The aim of this study was to evaluate morphological changes in motor cortices according to plasticity properties through voluntary exercise exposure. A total of 20 Wistar rats were evaluated at 90 postnatal days. The rats were separated in two groups, one of them (n=10) housed in standard vivarium cages, and the second group (n=10) in a cage containing an exercise wheel to implement voluntary aerobic exercise. The housing was adapted from P21 to P90. At P90 days, both groups were evaluated using rotarod for 4 consecutive days to assess motor coordination. After the behavioral evaluation, the rats were euthanized with an overdose of pentobarbital and perfused with paraformaldehyde for brain tissue fixation and collection. Immunostaining analysis was performed for both motor cortices (Bregma 0.48 mm) with synaptophysin antibody. Finally, a statistical analysis was performed to compare the groups. This protocol was approved by the bioethics committee of the Institute of Neurobiology at UNAM. Results: Through the statistical analysis of the rotarod test we didn't find a statistical significance in average time (t=-0.255, p=0.799) and in mean_speed (-0.006, p= 0.996). According to the synaptophysin expression, we found a significant difference in M1 (t= 2.146, p=0.041) and M2 (t= -2.77, p=0.011). Conclusions: The brains of exercised rats showed greater expression of synaptophysin in both motor cortices. However, no significant values were found in the RR test, this could be explained as this regimen of exercise has a clear effect in microstructural changes, but not enough in motor coordination, since all the subjects were healthy rats.

Disclosures: J.I. Alfaro-Moreno: None. **E.G. González-Pérez:** None. **S. Alcauter:** None. **C.J. Carranza-Aguilar:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.01/B50

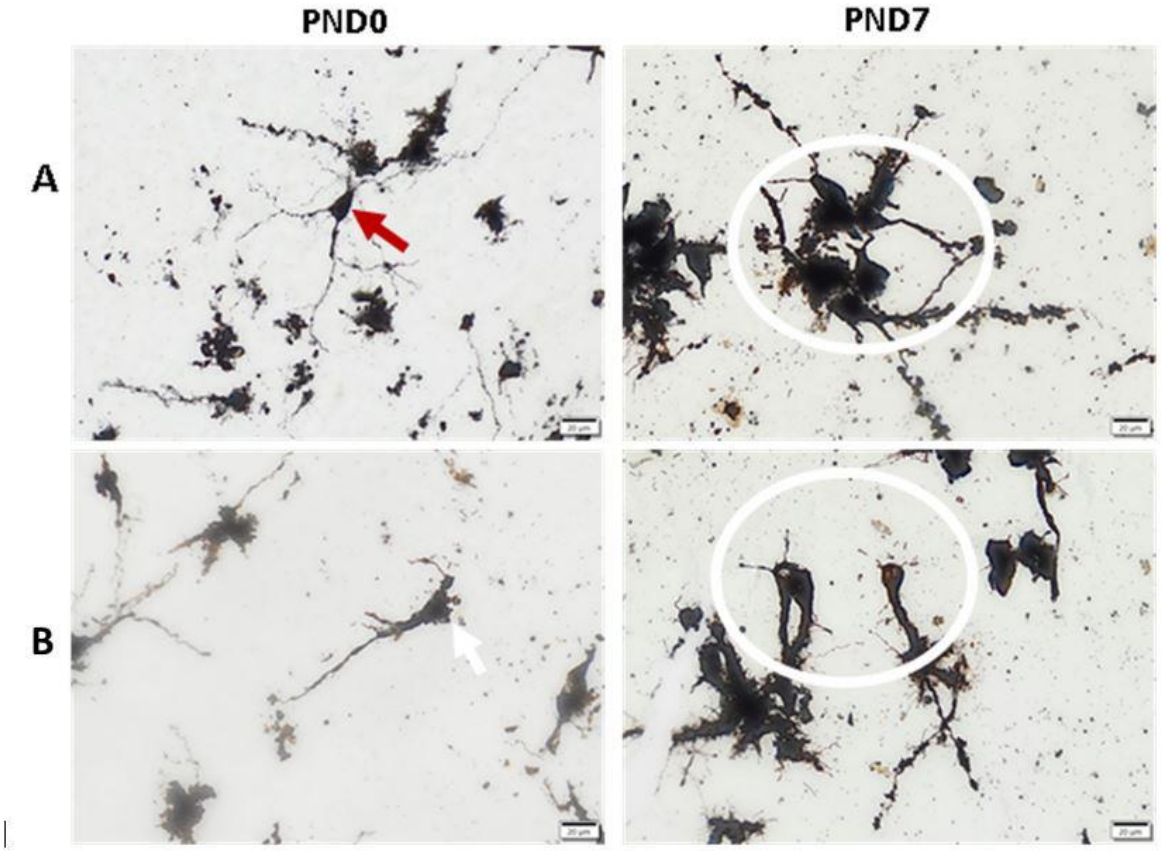
Topic: B.05. Synaptic Plasticity

Support: CARTA
TETFUND

Title: Prenatal kolanut consumption provokes immediate and later-life hippocampal morphplogical aberration and decrease in arborization and synaptic density in Sprague Dawley rat

Authors: *F. A. ATIBA[1], P. NKOMOZEPI[2], E. MBAJIORGU[3], A. O. IHUNWO[4];
[1]Univ. of Ibadan, Ibadan, Nigeria; [2]Human Anat. and Physiol., Univ. of Johannesburg, Johannesburg, South Africa; [3]Sch. of Anatom. Sci., Univ. of the Witwatersrand, Johannesburg, South Africa; [4]Univ. of Witwatersrand, Johannesburg, South Africa

Abstract: Background: kolanut is one of the snacks taken by pregnant women to prevent morning sickness symptoms. However, it is uncertain if prenatal exposure to kolanut consumption will alter the hippocampal physiology and then induces to oxidative stress, alteration in cholinergic activities and changes in morphology. The aim of this study was to evaluate the consequences of prenatal exposure to kolanut consumption on arborisation of the dendrites and morphological changes in the hippocampus of the Sprague Dawley rats.**Method:** Sprague Dawley pregnant rats were exposed to 400 mg/kg kolanut consumption from first day until parturition. Offspring were grouped as postnatal day (PND) 0, 7, 21, 56 and 70 in both control and experimental groups. Brain sections were processed for malonaldehyde (MDA), acetylcholine (Ach) and Brain-derived Neurotrophic Factor (BDNF) measurement and Golgi-cox impregnation staining for morphology assessment.**Results:** Prenatal kolanut consumption exacerbated oxidative stress, increased the level of BDNF expression and down-regulated acetylcholine release in rat hippocampus at the different PNDs. The total number of synaptic densities, soma (cell body) density and diameter, dendritic spine density, length, and branches at CA1, CA2, CA3 and DG were significantly reduced. Additionally, prenatal kolanut consumption reduced arborization of the dendrites and dendritic constriction and fragmentation, cause loss of spines, alteration in spine morphology across PNDs.**Conclusion:** Therefore, prenatal kolanut consumption during pregnancy has anti-neuroprotective effect by inducing oxidative stress, altering cholinergic system activity, stimulating over-expression of BDNF protein, and concomitantly causing changes in morphology of the hippocampal neurons.



Disclosures: **F.A. Atiba:** None. **P. Nkomozepi:** None. **E. Mbajiorgu:** None. **A.O. Ihunwo:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.02/B51

Topic: B.05. Synaptic Plasticity

Support: NSERC RGPIN-2015-05571, RGPIN-2024-05516
CIHR PJT-159779
ExCELLS 23-S2
NIPS 22-161, 23-155, 24-127

Title: Modeling the impacts of sleep history dependent structural plasticity of astrocytic processes on glutamatergic transmission at synapses to lateral hypothalamic orexin neurons

Authors: *C. SOZUER[1], V. PANDEY[2,3], Y. KUBOTA[3,4], K. SEMBA[1];
[1]Dept. of Med. Neurosci., Dalhousie Univ., Halifax, NS, Canada; [2]Fujita Hlth. Univ., Toyoake, Japan; [3]Natl. Inst. Physiol Sci. (NIPS), Okazaki, Japan; [4]Ctr. for Brain Sci., RIKEN, Wako, Japan

Abstract: Our previous work using volume electron microscopy (vEM) showed that astrocytic processes near synapses to orexin neurons undergo structural remodeling after sleep deprivation (Semba et al., 2023, SfN). To investigate whether this structural remodeling can explain our previous electrophysiological findings (Briggs et al., 2018, JNeurosci), we computationally modeled postsynaptic currents at tripartite synapses to orexin neurons under different conditions of astrocytic structural remodeling, glutamate transporter surface density, and synapse geometry. We employed Monte-Carlo Markov Chain simulations to model vesicular release and diffusion of glutamate in the extracellular space, while kinetic models of AMPA receptors were used to model excitatory postsynaptic currents under different conditions of astrocyte structure. Simulation results elucidated that the immediate and strongest effects of astrocytic structural plasticity are on the decay rates of glutamate concentration in the synaptic cleft and the decay rates of postsynaptic currents and that sleep deprivation lowered decay rates. We found changes in decay rates of glutamate concentration to be most effective under high-affinity presynaptic inhibition mechanisms. Because synaptic terminals at orexin neurons express high-affinity inhibitory group III mGluRs (Briggs et al., 2018, JNeurosci), these results point to remodeling as a potential mechanism for inducing presynaptic inhibition. The results therefore validate structural remodeling as a potential mechanism for our previous electrophysiological findings, which show that synapses at orexin neurons undergo presynaptic inhibition after sleep deprivation. Furthermore, under physiological rates of astrocytic glutamate transport, we found structural remodeling to have a greater influence on glutamate diffusion, and by extension presynaptic inhibition, than the diffusion of glutamate transporters on the cell membrane of

astrocytes, an alternative mechanism for astrocytic glutamate regulation. The sensitivity of these mechanisms to nanoscale distances between astrocytic processes and synaptic clefts underlines the importance of vEM in investigating synaptic mechanisms.

Disclosures: C. Sozuer: None. **V. Pandey:** None. **Y. Kubota:** None. **K. Semba:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.03/B52

Topic: B.05. Synaptic Plasticity

Support: KAIST-funded Global Singularity Research Program for 2022
National Research Foundation of Korea grant funded by the Korean government (MSIT) (no. 2020R1A2C301474213)
NIH grant DP1MH119428
IBS-R001-D2

Title: Real-time visualization of structural dynamics of synapses in live cells in vivo

Authors: *S. SON[1], K. NAGAHAMA[2], J. LEE[3], K. JUNG[4], C. KWAK[5], S. LEE[6], W. HEO[7]; [1]Ctr. for Cognition and Sociality, IBS, Dejeon, Korea, Republic of; [2]Neurosci., Johns Hopkins Univ., BALTIMORE, MD; [3]KAIST, Daejeon, Korea, Republic of; [4]Neural Dynamics, Allen Inst. for Neural Dynamics, Seattle, WA; [5]Ctr. for Cognition and Sociality, Inst. for Basic Sci. (IBS), Deajeon, Korea, Republic of; [6]Ctr. for Cognition and Sociality, Inst. for Basic Sci. (IBS), Daejeon, Korea, Republic of; [7]Dept. of Biol. Sci., Korea Advanced Inst. in Sci. and Technol. (KAIST), Daejeon, Korea, Republic of

Abstract: The structural plasticity of synapses is a fundamental mechanism regulating brain functions, yet methods for assessing synaptic dynamics *in vivo* have been limited. Here, we developed ‘SynapShot’—a method for visualizing intact synapses by combining dimerization-dependent fluorescent proteins (ddFPs) with engineered synaptic molecules. SynapShot is compatible with optogenetic techniques and enables real-time monitoring of structural synaptic changes in the mouse brain during primitive and higher-order behaviors.

Disclosures: S. Son: None. **K. Nagahama:** None. **J. Lee:** None. **K. Jung:** None. **C. Kwak:** None. **S. Lee:** None. **W. Heo:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

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Program #/Poster #: PSTR008.04/B53

Topic: B.05. Synaptic Plasticity

Support: JSPS Grants-in-Aid JP21H05171, JP21H05176
JST Moonshot R&D Grant JPMJMS2021
AMED Multidisciplinary Frontier Brain and Neuroscience Discoveries (Brain/MINDS 2.0) JP24wm0625001

Title: Microglia-mediated actions of noradrenaline on spine enlargement and learning in the medial prefrontal cortex

Authors: *H. OMI, M. TAJIRI, T. SAWADA, S. YAGISHITA;
Grad. Sch. of Med., The Univ. of Tokyo, Tokyo, Japan

Abstract: Dendritic spines undergo structural plasticity during learning in the neocortex of adult mice and noradrenaline (NA) is known to regulate learning in the mPFC. However, the exact signaling pathway that leads to activity-dependent spine enlargement in the neocortex remains unclear. To investigate spine enlargement in single spines of layer 5 pyramidal neurons in an acute slice preparation from the medial prefrontal cortex (mPFC) of mice, we applied a spike-timing-dependent plasticity protocol (STDP) with two-photon uncaging of glutamate. We found that NA enhanced spine enlargement in a β2, but not β1 adrenoreceptor-dependent manner, which are Gs-coupled receptors mainly expressed in the microglia and pyramidal neurons, respectively. Pharmacological inhibition of microglia-specific phosphodiesterase 3, which mediates activation of microglial β2 receptor downstream signaling, also facilitated spine enlargement in the absence of NA. STDP stimulation resulted in spine enlargement in juvenile mice (P16-21), but not in young adult mice (P35-45). Pharmacological ablation of microglia allowed spine enlargement even in young adult mice. NA-dependent spine enlargement was blocked by chemogenetic inhibition of cAMP signaling, specifically targeting microglia. These results indicate that microglia suppress spine enlargement in the adult mPFC and noradrenaline gate plasticity through disinhibition of the microglia-dependent mechanism. We further explored the behavioral relevance of this mechanism in an mPFC-dependent task of observational threat conditioning (OTC). We found a tonic noradrenaline increase in the mPFC during observation of threatened demonstrator mice. Microglial ablation and inhibition of CaMKII in the mPFC enhanced and reduced memory formation, respectively. In a pathological model, social defeat stress reduced NA-dependent spine enlargement and memory formation in OTC, so we now test whether manipulation targeting the microglia synaptic modulation pathway rescued the compromised memory formation. Overall, our findings provide new insights into the mechanisms of memory formation in the mPFC through the noradrenaline- and microglia-mediated synaptic mechanism, along with its vulnerability to chronic stress.

Disclosures: H. Omi: None. **M. Tajiri:** None. **T. Sawada:** None. **S. Yagishita:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.05/B54

Topic: B.05. Synaptic Plasticity

Support: NIMH Grant R01MH127423

Title: Transcriptome analysis provides insight into the role of the epigenetic reader PHF21B in modulating murine synaptic plasticity

Authors: *Y. HUANG, J. HE, Q. MA, H. RUAN, J. LICINIO, M.-L. WONG;
Psychiatry and Behavioral Sci., State Univ. of New York Upstate Med. Univ., Syracuse, NY

Abstract: Introduction: Synaptic dysfunction, the outcome of perturbations in physiological synapse structure and function, is a manifestation of several neurobehavioral and neurological disorders. A major therapeutic challenge for synaptic dysfunction lies in uncovering the upstream regulatory factors controlling synaptic processes. Plant homeodomain finger protein 21B (PHF21B) is a member of the histone demethylases superfamily that functions as an epigenetic reader whose dysfunctions are implicated in neurological disorders. Albeit essential, little is known about the molecular mechanisms linking PHD protein deficits to disease. **Methods:** To address this, we generated a PHD finger protein 21B-depleted (Phf21b-depleted) mutant CRISPR mouse model ($Phf21b^{\Delta4/\Delta4}$) to examine Phf21b's roles in the brain. Next, we performed genome-wide transcriptome profiling by using hippocampal tissues from the $Phf21b^{+/+}$ and $Phf21b^{\Delta4/\Delta4}$ animals. Sequencing was done on NextSeq 500 (Illumina) and data analysis were conducted using the Linux and R software environments, including FastQC (v0.11.8), Trimmomatic (v0.39), STAR aligner (v2.7.3a), featureCounts (v1.6.4), edgeR (v3.28.1) and clusterProfiler (v4.6.2) packages. **Results:** A set of 378 differentially expressed genes (DEGs) were identified with an FDR of less than 0.05 and a |FC|>1.5-fold. These DEGs were enriched for synaptic processes, including synaptic signaling, neuropeptide signaling, regulation of exocytosis, regulation of neurotransmitter, ion channel activity, gated channel activity and neuromuscular synaptic transmission. We further examined neuronal synapses in the $Phf21b^{\Delta4/\Delta4}$ and $Phf21b^{+/+}$ hippocampus via Golgi staining. Similar numbers of dendritic spines per unit length were observed in $Phf21b^{\Delta4/\Delta4}$ and $Phf21b^{+/+}$ hippocampal neurons. However, the $Phf21b^{\Delta4/\Delta4}$ neurons had a larger proportion of thin spines than the $Phf21b^{+/+}$ neurons. **Conclusion:** The discovery that PHF21B is a key regulator of a sizable group of synaptic genes is meaningful to expanding the knowledge of epigenetic mechanisms of synaptic plasticity.

Disclosures: Y. Huang: None. **J. He:** None. **Q. Ma:** None. **H. Ruan:** None. **J. Licinio:** None. **M. Wong:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.06/B55

Topic: B.05. Synaptic Plasticity

Support: NSFC Grant 32130044
NSFC Grant T2241002

Title: Functional axonic spines form in lateral septum neurons

Authors: *H. YANG[1], Y. SHU[2], K. WANG[1];
[1]Inst. for translational brain Res., Shanghai, China; [2]Inst. for Translational Brain Res., Fudan Univ., Shanghai, China

Abstract: Synapses at axon initial segment (AIS), the site of action potential (AP) generation, are believed to have crucial roles in regulating neuronal spiking activity. While GABAergic synapses onto the AIS of cortical pyramidal cells have been extensively studied, the existence and function of glutamatergic synapses at the AIS remain poorly understood. In this study, we conduct whole-cell recording, two-photon imaging, and *post hoc* staining of the recorded neurons in dorsal lateral septum (dLS) of adult male mice. We find a large proportion of dLS neurons form axonic spines at the AIS, with an average of ~3 spines per neuron. Scanning electron microscopy (SEM) reveal the ultrastructure of these axonic synapses, with characteristic presynaptic structures such as neurotransmitter vesicles and active zones, formed on the head and the neck of axonic spines. At the postsynaptic site, the axonic spines also show typical postsynaptic density of glutamatergic synapses. SEM with ankyrin G (AnkG) immunostaining shows that the axonic synapses form at the AnkG-stained AIS segment and the immunosignals can extend to the neck but not the head of axonic spines. Consistent with the electron microscopic results, two-photo MNI-glutamate uncaging at the axonic spines evokes excitatory postsynaptic potentials (EPSPs) with similar amplitudes and kinetics of EPSPs evoked at the dendritic spines. Further pharmacological experiments reveal that both AMPA and NMDA receptors contribute to the occurrence of axonic spine EPSPs. In agreement with the role of NMDA receptors in mediating the spike-timing-dependent plasticity, pairing glutamate uncaging with the generation of APs causes a substantial and long-term decrease in the length of axonic spine neck, while unpaired stimulations can't produce such synaptic plasticity. Together, the results provide clear evidence for the formation of glutamatergic axonic spines at the AIS of lateral septum neurons, and show that these axonic spines are functional and possess long-term plasticity. These glutamatergic spines at the strategic location for AP initiation may strongly regulate cellular excitability and participate in neuronal computing.

Disclosures: H. yang: None. **Y. Shu:** None. **K. Wang:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.07/B56

Topic: B.05. Synaptic Plasticity

Support: FR-21-4759

Title: The effect of propionic acid on the ultrastructure of the hippocampus and prefrontal cortex of the rat brain: electron microscopic morphometry of synaptic compartment.

Authors: *N. JAPARIDZE[1,2];
[1]Ivane Beritashvili Ctr. of Exptl. Biomedicine, Tbilisi, Georgia; [2]School of Medicine, New Vision University, Tbilisi, Georgia

Abstract: Nadezhda Japaridze[1,2], Nino Pochkhidze[1,3], Mzia Zhvania[1,31]Laboratory of Ultra – and Nanoarchitectonics of the Brain, Ivane Beritashvili Center of Experimental Biomedicine[2]New Vision University[3]School of Natural Sciences and Medicine, Ilia State University
The autism spectrum disorder (ASD) is a group of multifactorial neurodevelopmental disorders with the highly heterogeneous etiology. Molecular, cellular and functional studies of ASD experimental models have revealed that the different aspects of synapses (formation, elimination, transmission and plasticity) and synaptic dysfunctions can at least partially have been connected with the pathogenesis of ASD. That is why recent studies of our group studying various behavioral responses to propionic acid (PPA) in an experimental animal model have focused on the ultrastructure of the brain tissue and in particular the fine details of the synapses of the autistic brain. We previously found that a single intraperitoneal (ip) administration of PPA (175 mg/kg) caused transient (mostly) or permanent changes in neurons, glial cells, and synaptic connections of the CA1 region of the hippocampus and medial prefrontal cortex. In the present study, we demonstrate the effects of PPA on various structural parameters of axodendritic synapses in the hippocampus and prefrontal cortex using the same experimental conditions. The length of synaptic active zone, the area of presynaptic and postsynaptic mitochondria, the distance between presynaptic mitochondria and presynaptic cell membrane, the distance between postsynaptic mitochondria and postsynaptic density, and the opening diameter of neuronal porosome complex and its depth were evaluated. Our results demonstrate that postsynaptic mitochondria of the hippocampus and prefrontal cortex are the mostly affected by PPA treatment. In general, our results show that even small dose of PPA, which produces only superficial effects on cognitive functions, is able to alter the synapse architecture in brain regions involved in cognition. This work is supported by Shota Rustaveli National Science Foundation Grant #FR-21-4759.

Disclosures: N. Japaridze: None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.08/B57

Topic: B.05. Synaptic Plasticity

Title: Ketamine-induced structural plasticity in dendritic spines of the dorsomedial prefrontal cortex is hindered in aged mice

Authors: *I. FERNANDEZ UGIDOS[1,2], J. CALVO IGLESIAS[1,2], R. MOSTANY[1,2];
[1]Tulane Univ., New Orleans, LA; [2]Tulane Brain Inst., New Orleans, LA

Abstract: Ketamine has recently been approved by the FDA as a promising approach for treatment-resistant depression. However, its effectiveness diminishes in the elderly, requiring higher doses and more frequent administration to achieve the same effects than in young or adult patients. Despite the higher prevalence of depression in older individuals, the specific mechanisms behind ketamine's reduced efficacy with aging remain unexplored. Ketamine's antidepressant mechanism of action is believed to be based on its ability to facilitate the formation of new neuronal connections in the prefrontal cortex. Specifically, the formation of new dendritic spines has been directly associated with the long-lasting antidepressant effect of ketamine. Our previous studies show that aging decreases the plasticity response at the level of dendritic spines in somatosensory cortex, thus we hypothesize that the induction of structural plasticity by ketamine in the dorsomedial prefrontal cortex (dmPFC) will also be diminished with aging, preventing its anti-depressant effect. In our study, we analyzed the dendritic spine dynamics in the dmPFC pre- and post-ketamine administration (10 mg/kg, i.p) in young (3-5 months-old) and aged (18-22 months-old) Thy1-GFP mice. We also tested whether ketamine's plasticity effect is widespread or specific to certain brain regions by simultaneously analyzing the dendritic spine dynamics in the somatosensory cortex. Our results show that aging does not affect basal dendritic spine dynamics in layer 5 pyramidal neurons of the dmPFC. Interestingly, ketamine boosts the formation and reduces the elimination of dendritic spines in young adult mice, while neither of those effects is detected in aged mice. Furthermore, this effect is confined to the dmPFC, as ketamine fails to induce similar structural plasticity at the doses tested in the somatosensory cortex. These results evidence the reduced ketamine efficacy as an inductor of structural plasticity in aging and provide us with a model to study the molecular mechanism underlying the lack of its antidepressant effect and to test novel therapeutic interventions in the aging population.

Disclosures: I. Fernandez Ugidos: None. **J. Calvo Iglesias:** None. **R. Mostany:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.09/B58

Topic: B.05. Synaptic Plasticity

Title: The stability of the neuromuscular junction in the $apc^{min/+}$ mouse model of cancer-induced cachexia

Authors: *K. KOWAL[1], A. MOHIUDDIN[1], F. CARNIVELE[2], I. MARTINEZ-PENA Y VALENZUELA[3];
[1]Chicago Col. of Osteo. Med., Downers Grove, IL; [2]Chicago Col. of Pharm., Downers Grove, IL; [3]Physiol., Midwestern Univ., Downers Grove, IL

Abstract: Introduction: Cancer-induced cachexia is a complex multifactorial syndrome characterized by loss of muscle mass and function that affects up to 80% of cancer patients which contributes to the morbidity and mortality of the disease. Despite the extensive research on cancer cachexia, its exact etiology remains unknown. There is also no consensus on effective treatment for the loss of muscle mass, which subsequently impacts the tolerance and response to anti-cancer therapies. Furthermore, little is known about the effect of muscle wasting on the neuromuscular junction (NMJ), the vital synaptic connection between the motor neuron and skeletal muscle that is crucial for muscle function. Recent studies have shown that the NMJ is stable in cancer-induced cachexia. Since other muscle wasting conditions such as sarcopenia or muscle denervation result in alterations in the NMJ, we hypothesize that the environment of cancer-induced cachexia alters the NMJ.In this study, we analyze the stability of the NMJs from cachectic muscles during the initiation and progression of the muscle-wasting event. **Material and Methods:** We used the genetically engineered mouse model of colorectal cancer $Apc^{Min/+}$ which has shown cancer-induced cachexia, and their age-matched C57BL/6 controls. $Apc^{Min/+}$ mouse is an excellent animal model bearing multiple intestinal neoplasia, used to simulate human familial adenomatous polyposis and colorectal tumors. We used the toxin Alexa488™ α-bungarotoxin to specifically label nicotinic acetylcholine receptors (AChRs) present at the NMJ, and we analyzed the Sternomastoid, Gastrocnemius, Extensor Digitorum Longus, Soleus, and Diaphragm muscles from $Apc^{Min/+}$ and controls at 10, 16, and 24 weeks. The muscles were fixed in 4% paraformaldehyde and bathed with the toxin (5μg/ml, ~1 hour). Fluorescently labeled muscles were then imaged in an inverted fluorescence microscope to quantify fluorescence intensity and in the confocal microscope to assess changes in the NMJ. The area and the density of nAChRs were then analyzed using ImageJ. In addition, we performed histological techniques in the muscles from and at different ages. **Results:** We have found that all skeletal muscles analyzed are affected in the mouse model of cancer-induced cachexia, especially at 24 weeks of age. Muscles showed a decrease in both the nAChR density and the synaptic area. **Conclusions:** The decreased nAChR density and NMJ area in both fast and slow twitch muscles demonstrate postsynaptic NMJ alteration in cancer-induced cachectic mice.

Disclosures: K. Kowal: None. **A. Mohiuddin:** None. **F. Carnivele:** None. **I. Martinez-Pena y Valenzuela:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.10/B59

Topic: B.05. Synaptic Plasticity

Support: NRF-NRFF12-2020-0008

Title: Post-synaptic tau—redefining physiological functions of tau

Authors: *H. JIANG, R.-Y. HONG, J. NISHIYAMA;
Duke-NUS Med. Sch., Natl. Univ. of Singapore, Singapore, Singapore

Abstract: Research on microtubule-associated protein tau has focused largely on its pathological roles as it being a major component of neurofibrillary tangles in Alzheimer's disease and closely related to neurodegenerative diseases, but its physiological roles remain less explored. Tau was first defined to be an axonal protein by the immunostaining of Tau-1 antibody. However, there are several antibodies showing normal tau distribution in somatodendritic regions as well. The variation in tau distribution across functional compartments may relate with different epitope reactivity altered by post-translational modifications. Thus, the disputes over tau normal distribution is not yet settled. Here we report an endogenous labelling system by CRISPR/Cas9 knock-in method to visualize tau protein using tags (eg, HA), thus overcoming the issue of tau antibody heterogeneity. We show that tau distributes in both axonal and somatodendritic regions in normal mouse brain and primary hippocampal neurons. In contrast to other MAPs, tau is moderately accumulated in dendritic spines. Regarding the nanoscale distribution of tau, we report that tau is localized within the actin cytoskeleton system by using protein expansion microscopy. Functionally, knocking out tau leads to an impairment of structural long-term potentiation (sLTP) while rescuing it restores the sLTP. In addition, endogenous tau translocates to dendritic spines during glutamate uncaging-induced sLTP. To investigate the mechanism of how tau functions in synaptic plasticity, we developed a novel intramolecular Tau fluorescence resonance energy transfer (FRET) sensor, which can reveal the conformational changes of tau. Further investigating of the dynamic changes of this Tau FRET sensor is warranted to elucidate the detailed mechanism. In all, this study clarifies the normal distribution of tau protein in axonal and somatodendritic regions with novel methods and demonstrates the role of tau protein in sLTP while showing its translocation to dendritic spines during sLTP in live imaging for the first time. In addition, Tau FRET sensor would help to further reveal the conformational and dynamic changes of tau during sLTP. Our results also contribute to a thorough understanding of tau physiological role thus providing insight into its pathological changes.

Disclosures: H. Jiang: None. **R. Hong:** None. **J. Nishiyama:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.11/B60

Topic: B.05. Synaptic Plasticity

Support: JSPS KAKENHI Grant No. JP22K07864
Takeda Science Foundation

Title: Super-resolved 3D-STED microscopy reveals region-specific changes in excitatory synapses in the hippocampus of model mice of developmental disorders

Authors: *N. KOGANEZAWA[1,2,3], S. KATSUBE[3], T. SHIRAO[2], H. KAWABE[3];
[1]Computat. Biol. and Med. Sci., The Univ. of Tokyo, Tokyo, Japan; [2]AlzMed Inc., Tokyo, Japan; [3]Pharmacol., Gunma Univ. Grad. Sch. of Med., Maebashi, Japan

Abstract: The chemical synapse transmits information from one neuron to another neuron in the neuronal network in the brain. The efficacy of synaptic transmission changes by modifying the number or size of synapses dynamically in cognitive functions. Thus, morphological analyses of synapses are of particular importance in neuroscience research. In the current study, we applied super-resolved three-dimensional stimulated emission depletion (3D-STED) microscopy for the morphological analyses of synapses. This approach allowed us to estimate the precise number of excitatory and inhibitory synapses in the mouse hippocampal tissue. Using this method, we discovered a region-specific increase in excitatory synapses in a model mouse of autism spectrum disorder, *Neuroligin-3* KO. We detected an increase in excitatory synapses at the stratum oriens of hippocampal area CA1, although such an increase was not detected by conventional confocal microscopy. We further applied this method to a model mouse of Kaufman oculocerebrofacial syndrome (KOS), one of developmental disabilities. KOS is a severe autosomal recessive disorder characterized by general developmental delay with intellectual disability, hypocholesterolemia, and seizures. *Ube3b*, an E3 ligase gene, has been reported as the causative gene for KOS. Our previous report demonstrated a loss of murine *Ube3b* increases the number of dendritic spines at the age of three weeks, indicating that *Ube3b* is a negative regulator of synaptogenesis for the excitatory synapses in the early developmental stage. Here, using brain-specific conditional *Ube3b* knockout (*Ube3b* cKO) mice, we investigated the further role of *Ube3b* in the young adult period. Images from the hippocampal CA1 region were acquired with 3D-STED microscopy to estimate the excitatory synapse numbers. We found that the excitatory synapse density significantly decreased in *Ube3b* cKO as compared to the control. Together with our previous reports, our results indicate the novel role of *Ube3b* in the maintenance of synapse numbers in the young adult period. Our approach to estimating the synapse number will open a new field in developmental neuroscience.

Disclosures: N. Koganezawa: A. Employment/Salary (full or part-time):; AlzMed Inc.. **S. Katsube:** None. **T. Shirao:** A. Employment/Salary (full or part-time):; AlzMed Inc.. **H. Kawabe:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.12/B61

Topic: B.05. Synaptic Plasticity

Support: R21AG082230 to AF
AARF22973974 to AF
R01AG069433 to GT
R01AG073133 to GT

Title: Cognitive integrity in Non-Demented Individuals with Alzheimer's Disease Neuropathology is associated with remodeling of dendritic spines and increased levels of Pin1

Authors: J. GUPTARAK, P. SCADUTO, B. TUMURBAATAR, W.-R. ZHANG, D. JUPITER, G. TAGLIALATELA, ***A. FRACASSI**;
Univ. of Texas Med. Br., Galveston, TX

Abstract: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder leading to dementia. The existence of individuals who remain cognitively intact despite presenting histopathological signs of AD, here referred to as "Non-demented with AD neuropathology" (NDAN), suggests that some mechanisms are triggered to resist cognitive impairment. These individuals are distinguished by the presence of highly phagocytic microglia capable of clearing damaged synapses near plaques, thereby mitigating further damage to axons and dendrites. In this study, we conducted a comparative analysis of dendritic spine morphology in the post-mortem frontal cortex of NDAN individuals, AD patients, and age-matched healthy controls. Our investigation included an in-depth examination of synaptic structures both near and far from Aβ plaques, quantifying aspects such as dendrite length, diameter, spine density, and types. In addition, we expanded our research to investigate levels and distribution of Pin1, identified as a potential key player in the protective mechanisms against AD, influencing the regulation of dendritic spine formation and maintenance, tau phosphorylation, and mediation of Aβ toxicity. Not surprisingly, within 100 μm of Aβ plaques, significant synaptic toxicity was observed in all groups. However, in areas distal to plaques, NDAN exhibited significantly higher spine density than AD, suggesting the existence of a compensatory mechanism. We also measured the relative abundance of four spine types: mushroom, stubby, filopodia, and long thin, finding stubby spines to be the most common across all groups. Mushroom spines, the least dynamic, were significantly more abundant in AD compared to NDAN and control subjects. Conversely, NDAN individuals showed a higher density of more dynamic/immature and plastic spines, such as filopodia and long thin spines, than AD. These findings suggest that the rearrangement of dynamic dendritic spines in NDAN may underlie the ability of these individuals to replace damaged synapses and preserve cognitive integrity. Furthermore, our results revealed lower expression of Pin1 in AD patients than control and NDAN groups, across regions, proximal and distal to plaques. This finding suggests that reduced Pin1 expression in AD may contribute to the compromised synaptic integrity and plasticity observed in these individuals. This study thus sheds light on the potential mechanisms allowing NDAN individuals to retain cognitive function despite AD pathology, offering insights for future therapeutic strategies.

Disclosures: J. Guptarak: None. **P. Scaduto:** None. **B. Tumurbaatar:** None. **W. Zhang:** None. **D. Jupiter:** None. **G. Taglialatela:** None. **A. Fracassi:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.13/B62

Topic: B.05. Synaptic Plasticity

Title: Plastinogenic effects of ketamine and other NMDA receptor antagonists on primary mouse cortical neurons: establishing a platform for novel antidepressant discovery

Authors: *C. J. MALTBY[1], I. BARBIERO[2], J. KEALY[1], S. GATTI[3], Z. A. HUGHES[4], M. BIANCHI[1,5];
[1]Ulysses Neurosci. Ltd, Dublin, Ireland; [2]DBSV, Univ. of Insubria, Busto Arsizio, Italy; [3]McArthur and Associates GmbH, Basel, Switzerland; [4]Gilgamesh Pharmaceuticals, NY, NY; [5]Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland

Abstract: Clinical depression still represents a challenge to the field of psychiatry, with around 50% of patients experiencing little to no relief from current antidepressant drugs. The recent emergence of ketamine as a rapid-acting and long-lasting antidepressant has paved the way for other non-traditional compounds with novel mechanisms of action such as psychedelic drugs as potential therapeutics.
Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist dissociative anaesthetic widely used in human and veterinarian medicine as well as recreationally for its psychedelic-like effects. Ketamine's S-enantiomer induces rapid and lasting antidepressant effects and has received regulatory approval for use in clinician-guided treatment of depression. The exact molecular cascades preceding these antidepressant effects remain unclear, however, ketamine has been shown to induce synaptogenesis and dendritic growth in experimental models, suggesting possible plastinogenic mechanisms underlying its antidepressant effects.
Methods: This study aimed to investigate the plastinogenic effects of NMDA receptor antagonists (NAs), including ketamine, by examining the morphological changes induced in neurons. Primary mouse cortical neurons were cultured *in vitro* and treated with NAs for 24 h, followed by fixation with 4% paraformaldehyde at DIV10 for Sholl analysis of dendritic arborisation, or at DIV14 for analysis of dendritic spines by counting PSD95 positive puncta along MAP2 positive dendrites. Analyses were conducted by immunocytochemistry for MAP2 and MAP2 / PSD95 staining respectively.
Results: Exposure to NAs for 24 h at 3 µM or 10 µM was sufficient to induce a significant increase in overall dendritic branching between 20-40 µm and 80-90 µm from the soma when compared to a vehicle only control. Similarly, a significant increase in dendritic spine density was observed for both 3 µM or 10 µM NAs treatments, with ~50% increase in PSD95 positive puncta detected along the initial 30 µm segment of the secondary dendritic branches.
These data provide valuable insight into ketamine's ability to induce structural changes in neurons, which may underlie its rapid antidepressant effects. The results confirm the plastinogenic effects of ketamine both at the presynaptic and synaptic level and importantly, our work establishes a platform for testing novel compounds and assessing their potential to mimic or exceed the plastinogenic effects of ketamine. This is of particular importance for the initial screening of psychedelics or psychedelic-derivative drugs.

Disclosures: C.J. Maltby: A. Employment/Salary (full or part-time):; Ulysses Neuroscience Ltd. **I. Barbiero:** None. **J. Kealy:** A. Employment/Salary (full or part-time):; Ulysses Neuroscience Ltd. **S. Gatti:** None. **Z.A. Hughes:** A. Employment/Salary (full or part-time):; Gilgamesh Pharmaceuticals. **M. Bianchi:** A. Employment/Salary (full or part-time):; Ulysses Neuroscience Ltd.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.14/B63

Topic: B.05. Synaptic Plasticity

Support: NIH/NINDS R01 NS120746

Title: Role of TrkB.T1 in Astrocyte-Regulated Synaptic Morphology

Authors: *Y. PAN[1], X. WEI[2], K. NOEL[1], M. L. OLSEN[2];
[1]Virginia Technol., Blacksburg, VA; [2]Virginia Technol. Neurosci. PhD Program, Blacksburg, VA

Abstract: The tropomyosin receptor kinase B (TrkB), which serves as the receptor for Brain-derived neurotrophic factor (Bdnf), plays a crucial role in brain development and maturation. The central nervous system (CNS) expresses two main isoforms of the TrkB receptor: the full-length TrkB.FL and the truncated TrkB.T1, which lacks the tyrosine kinase domain. The specific functions of TrkB.T1 in the nervous system remain unclear. Our prior research suggests that the TrkB.T1 isoform, which is expressed at higher levels in human and mouse brain than TrkB.FL, is predominantly expressed in astrocytes and regulates their morphological maturation. Further, utilizing a simplified astrocyte-neuron co-culture model system we demonstrated that TrkB.T1 KO astrocytes do not support glutamatergic synaptogenesis. In the current study we generated an astrocyte specific genetic deletion of TrkB.T1 (Ald1h1l1-Cre x Trkb.T1 fl/fl). RNA-sequencing data and subsequent pathway analysis revealed differential gene expression and biological pathways associated with disrupted synaptogenesis during development in astrocyte TrkB.T1 mice relative to WT littermate controls. To investigate synaptic and astrocyte interactions, we applied a sparse labeling approach using fluorescently tagged AAV-hsynapsin-and AAV-GFAPabc1d.Lck-GFP (membrane tethered astrocyte GFP) to visualize astrocytes and neurons throughout the CNS. Studies using confocal imaging, to evaluate spine density, spine morphological analysis and astrocyte spine coverage in juvenile P14 and P28 primary motor and somatosensory cortex are ongoing to determine if astrocyte TrkB.T1 deletion impacts neuronal spine development.

Disclosures: Y. Pan: None. **X. Wei:** None. **K. Noel:** None. **M.L. Olsen:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.15/B64

Topic: B.05. Synaptic Plasticity

Support: T32GM142519
P30AG072931
R21AG068423
23AARG-1026776

Title: Local translation within dendritic spines and its roles in synaptic plasticity and memory

Authors: *A. GRETZINGER[1], B. BONE[2], J. PARK[1];
[1]Wayne State Univ., Detroit, MI; [2]Pharmacol., Wayne State Univ., Wixom, MI

Abstract: Protein synthesis is critical for learning and memory. Given that neurons exhibit a high degree of polarity and activity-dependent plasticity, compartment-specific translation is likely important to maintain synaptic proteins appropriately. Evidence indicates the presence of synapse-associated ribosomes in dendritic spines and local mRNA pools being translated by ribosomes in neurites. Several key proteins involved in maintaining the dendritic spine architecture are reported to be preferentially translated in the neuropil, such as PSD-95 and CaMKIIα. Additionally, dysfunctional spine architecture is observed in neurodegenerative disorders including Alzheimer's Disease, indicating a possible disturbance in dendritic protein homeostasis. Despite the accumulating evidence supporting local translation, its roles in synaptic plasticity and learning and memory remain elusive. To address this question, we generated a viral construct expressing a genetically encodable protein synthesis inhibitor designed to be targeted selectively to postsynaptic regions (postPSI). We validated the compartment-specific inhibition of protein synthesis using Puro-PLA assays in cultured hippocampal neurons and puromycilation assays of the mouse hippocampus. Using these molecular approaches, we report that inhibition of local dendritic translation prevents synaptic plasticity of hippocampal neurons and fear memories of mice. Furthermore, utilizing our proteomics approach combined with postPSI, we profile potential substrates that may rely on local dendritic translation and play roles in plasticity and memory. These data provide molecular insights into mechanisms underlying learning and memory, which are of benefit in understanding the progression of many dementia-associated neurodegenerative disorders.

Disclosures: A. Gretzinger: None. **B. Bone:** None. **J. Park:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.16/B65

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R15DA038092
NIH Grant R15DA049260

Title: Cocaine Blocks a Novel Form of iLTD, but not iLTP of Inhibitory Inputs to VTA GABA Neurons

Authors: *S. B. HOFFMAN[1], B. WU[2], H. UREY[1], J. G. EDWARDS[3];
[1]Brigham Young Univ., Provo, UT; [2]Cell, Brigham Young Univ., Provo, UT; [3]PDBio, Brigham Young Univ., Provo, UT

Abstract: The ventral tegmental area (VTA) is an essential part of the reward system that under maladaptive conditions facilitates drug seeking and addiction behaviors. Synaptic plasticity, underlying normal reward learning and memory, is altered by drugs of abuse. Our research extends the understanding of synaptic plasticity to inhibitory networks. We previously examined iLTP and identified a novel form of iLTD at GABAergic inputs to VTA GABA synapses. While iLTD is $GABA_B$ receptor-dependent, the iLTP was more complex, being only partially contingent upon N-methyl-D-aspartic acid receptor (NMDAR) activity. This partial dependency hints at the existence of additional mechanisms potentially driving the induction of iLTP that we explore in this study. Here we determined that iLTP is not cholecystokinin (CCK)-dependent as bath application of CCK_2R antagonist LY225910 (1μM) did not affect the observed iLTP or iLTD (iLTP: $p<0.0001$, compared to baseline, ANOVA, n=7; iLTD: $p<0.0001$ compared to baseline, ANOVA, n=6). In addition, though the nitric oxide (NO) pathway can change GABA transmission, it is not necessary for iLTP induction; potentiation induced by the NO donor SNAP was occluded by the 5Hz stimulus (Occlusion: $p=0.092$, compared to baseline, ANOVA, n=3). Since VTA GABA neurons receive inhibitory input from both inside and outside the VTA, we hypothesize that plasticity type could be due to unique GABAergic input sources. To test this hypothesis, we optogenetically drove three different GABAergic inputs to the VTA, the Lateral Hypothalamus (LH), the rostromedial tegmental nucleus (RMTg) and VTA interneurons. Activation of GABAergic LH and RMTg terminals induces iLTP in response to an optical 5Hz stimulus (iLTP, LH to VTA: $p<0.0001$ compared to baseline, ANOVA, n=14; iLTP, RMTg to VTA: $p<0.0001$ compared to baseline, ANOVA, n=6), while activation of the VTA interneurons produces iLTD with the same stimulus (iLTD, VTA to VTA, $p<0.0001$ compared to baseline, ANOVA, n=12). Additionally, we observed that both acute and chronic cocaine exposure prevented the occurrence of iLTD. Chronic cocaine and acute cocaine treatment both prevent 5Hz-induced iLTD/iLTP (Chronic: no plasticity group: $p=0.1937$, compared to baseline, ANOVA, n=7, and $p<0.0001$ compared to control iLTD; iLTP: $p<0.0001$, compared to baseline, ANOVA, n=7. Acute: no plasticity group: $p=0.8362$, compared to baseline, ANOVA, n=7, and $p<0.0001$ compared to control iLTD; iLTP: $p<0.0001$, compared to baseline, ANOVA, n=9). Our study provides novel insights into the mechanisms of synaptic plasticity within the VTA, emphasizing the role of GABAergic neurons in the brain's response to drugs of abuse.

Disclosures: S.B. Hoffman: None. **B. Wu:** None. **H. Urey:** None. **J.G. Edwards:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.17/B66

Topic: B.08. Epilepsy

Support: CSIR (Fellowship No. (09/0141(12456)/2021-EMR-I), New Delhi, India.
Department of Biotechnology (DBT) (BT/PR10968/MED/30/1326/2014), New Delhi, India.
ICMR grant (BMS/adhoc/137/2022-23), New Delhi, India.

Title: Metaplasticity in epileptiform induced slices impairs long term depression in the rat hippocampal CA1 synapses

Authors: *Z. RANA[1], P. PUNNAKKAL[2];
[1]Biophysics, Post Grad. Inst. of Med. Educ. and Res., Chandigarh, India; [2]Biophysics, Post Grad. Inst. of Med. Educ. and R, Chandigarh, India

Abstract: Temporal lobe epilepsy (TLE) represents the predominant form of epilepsy in humans, frequently accompanied by cognitive dysfunction and challenges in memory consolidation. To elucidate alterations in the cellular mechanisms of memory within TLE, we investigated long-term depression (LTD) within Schaffer-collateral (Sc) CA1 synapses in an epilepsy model. While prior research extensively explored long-term potentiation (LTP) in both patient samples and animal models, LTD received comparably lesser attention in epilepsy research. Herein, we induced epileptiform activity in rat hippocampal slices via magnesium-free high-potassium (7.5 mM K^+) artificial cerebrospinal fluid (HK-ACSF) and characterized the LTD in Sc-CA1 synapses. Our findings reveal that epileptiform activity affects LTD and depotentiation within these synapses. Specifically, in control slices, NMDA application, induced chemical LTD (c-LTD) in Sc-CA1 synapses, whereas epileptiform activity led to a slow onset potentiation. Moreover, LTD induction via 1 Hz, 900 pulses induced LTP instead of LTD in epileptiform induced slices. The plasticity induced was NMDA receptor dependent. Furthermore, the observed polarity changes in the synaptic plasticity of epileptiform induced slices was sensitive to GluN2B antagonists ifenprodil and Ro 25-6981. Collectively, our data suggest that epileptiform-induced metaplasticity inhibits LTD in Sc-CA1 synapses and it is mediated by GluN2B subunit containing receptors.

Disclosures: Z. Rana: None. **P. Punnakkal:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.18/B67

Topic: B.05. Synaptic Plasticity

Support: P50-MH132775

Title: Oligodendrocyte myelin glycoprotein impairs dendritic arbors via schizophrenia risk gene TRIO

Authors: *J. M. CHRISTIANSEN[1], E. L. PARNELL[2], M. L. MACDONALD[3], P. PENZES[1], R. A. SWEET[4], M. J. GRUBISHA[3];
[1]Neurosci., [2]Physiol., Northwestern Univ., Chicago, IL; [3]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [4]Dept Psychiatry, Univ. of Pittsburgh Dept. of Psychiatry, Pittsburgh, PA

Abstract: TRIO is a gene that has been implicated in neurodevelopmental disorders such as schizophrenia, autism spectrum disorder, and intellectual disability. The Trio family of proteins plays a crucial role in neuronal outgrowth, dendritic arborization, and synaptic plasticity. Previous research has shown that variants and altered expression in Trio contribute to the development of NDDs. Here we dissect a signaling pathway involving the Oligodendrocyte Myelin Glycoprotein (OMGp) that has been implicated in regulating neurite outgrowth during neurodevelopment. Unbiased phospho-proteomic analysis after OMGp stimulation revealed Trio as an effector of OMGp signaling. Phosphomimetic Trio9L was deficient in RAC1 catalytic activity and was unable to drive neurite outgrowth compared to wild type protein. Moreover, phosphonull constructs blocked the ability of OMGp to drive dendritic outgrowth and complexity. Additionally, we isolate a role for different Trio isoforms to drive synaptogenesis downstream of OMGp. Together, these results highlight the ability of OMGp to regulate neuronal complexity and connectivity by potently inhibiting the RAC1 catalytic activity of Trio. As dysregulation of the OMGp receptor and Trio have been linked to schizophrenia risk, these results provide a potential mechanism contributing to the emergence of neuronal dysfunction and schizophrenia symptomology during adolescence.

Disclosures: J.M. Christiansen: None. **E.L. Parnell:** None. **M.L. MacDonald:** None. **P. Penzes:** None. **R.A. Sweet:** None. **M.J. Grubisha:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.19/B68

Topic: B.05. Synaptic Plasticity

Support: R01NS114977

Title: Impairment of synaptic plasticity caused by the autism and schizophrenia associated 16p11.2 duplication.

Authors: *M. FORREST[1], N. H. PIGUEL[2], L. E. DIONISIO[1], V. BAGCHI[1], P. PENZES[2]; [2]Neurosci., [1]Northwestern Univ., Chicago, IL

Abstract: Synaptic plasticity is a fundamental mechanism thought it underlie learning and memory, and could be disrupted in neuropsychiatric disorders. The 16p11.2 duplication is genetic risk factor that strongly predisposes to psychiatric and cognitive disorders such as autism, schizophrenia and intellectual disability. The duplication consists of a 600kb region on chromosome 16, including 30 genes, with poorly defined effects on brain function and plasticity. Here, we used models of 16p11.2 duplication to investigate the impact of this genetic variant on synaptic structural plasticity. We find alterations to dendritic arbors and dendritic spine morphology in 16p11.2 duplication neurons. We also observe a change in the abundance of AMPA and trafficking of receptors within dendritic spines. Using homoeostatic plasticity paradigms, we show that neurons with the 16p11.2 duplication have disrupted plasticity of synapses and dendritic arbors. Finally, we show that normalizing PRRT2 (a protein encoded in the 16p11.2 region) levels to WT rescues phenotypes associated with structural plasticity. Our work suggests that aberrant plasticity could contribute to the etiology of neuropsychiatric disorders.

Disclosures: M. Forrest: None. **N.H. Piguel:** None. **L.E. Dionisio:** None. **V. Bagchi:** None. **P. Penzes:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.20/B69

Topic: B.05. Synaptic Plasticity

Support: R01MH107182
NCI CCSG P30 CA060553

Title: Using expansion microscopy to visualize AnkG-190 nanodomains and their association with dendritic spine morphology.

Authors: *N. H. PIGUEL[1], M. DOS SANTOS[1], B. ECKMAN[2], P. PENZES[3]; [1]Northwestern Univ., Chicago, IL; [2]Northwestern Univ., Evanston, IL; [3]Neurosci., Northwestern Univ., Chicago, IL

Abstract: The ANK3 gene is associated with a variety of neuropsychiatric and cognitive disorders. It encodes the protein ankyrin-G (AnkG), a multifunctional scaffold protein with several isoforms: the 480 kDa and 270 kDa isoforms have important roles at the axon initial segment and node of Ranvier whereas the function of the 190 kDa isoform (AnkG-190) appears more specialized in the dendritic area of glutamatergic neurons. We have previously described AnkG-190's roles in dendrite complexity and dendritic spine morphology and how its palmitoylation is essential to maintain its cellular localization and function. Moreover, the

presence of AnkG-190 in the dendritic spine neck seems important for spine enlargement during Long Term Plasticity. In this project, we investigate AnkG-190 and some of its partners' localization at a nanoscopic scale in the dendrite and the dendritic spine using expansion microscopy to uncover AnkG-190 pattern and how it affects dendritic spine morphology at a super-resolution.

Disclosures: N.H. Piguel: None. **M. Dos Santos:** None. **B. Eckman:** None. **P. Penzes:** None.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.21/B70

Topic: B.05. Synaptic Plasticity

Support: NIH MH071316

Title: Mutations in KALRN are linked to neurodevelopmental disorders

Authors: *E. PARNELL, J. CHRISTIANSEN, P. PENZES;
Neurosci., Northwestern Univ., Chicago, IL

Abstract: KALRN is a key regulator of synaptic plasticity, dendritic arborization and neurodevelopment. Numerous studies have linked mutations in the KALRN gene to neurodevelopmental disorders such as schizophrenia and intellectual disability. To comprehensively assess the role of KALRN in neurodevelopment, we have assembled a cohort of patients with mutations in KALRN through a network of clinicians. These patients carry mutations in a range of functional domains, and present with several neurological disorders and brain malformations. These mutations cluster in the 3' of KALRN, implicating the long form, Kalirin12, in neurodevelopment. Kalirin12 is expressed early in neurodevelopment, and the functions of its 3' domains are largely unknown. Here we employ biochemical analysis to inform on the function of these domains on neuroarchitecture, as well as the effect of disease-linked mutations on the function of these domains, and of Kalirin12 on neurodevelopment. This analysis will go hand in hand with KALRN-KO mouse brain analyses to assess the functional effects of Kalirin12 loss on neuroanatomy. Together we link KALRN mutations to neuronal dysfunction and brain structural abnormalities, with the goal to facilitate the formation of a KALRN advocacy and support group and drive the study and treatment of KALRN-linked neurodevelopmental disorders.

Disclosures: E. Parnell: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Synaptomed, Inc. **J. Christiansen:** None. **P. Penzes:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Synaptomed, Inc.

Poster

PSTR008: Structural Plasticity: Synapses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.22/B71

Topic: B.05. Synaptic Plasticity

Support: NIH Grant NS136753
NIH Grant NS130108

Title: Synaptic defects and homeostatic responses caused by mitochondrial complex I dysfunction

Authors: B. MALLIK[1], *C. FRANK[2];
[1]Univ. of Iowa, IOWA CITY, IA; [2]Univ. of Iowa, Iowa City, IA

Abstract: Neurons and their synapses require high amounts of energy to sustain normal levels of activity. Mitochondria are the main energy source, producing ATP via oxidative phosphorylation. In turn, oxidative phosphorylation proceeds through the action of large protein complexes, like Mitochondrial Complex I (MCI). But much work shows that mitochondrial components in neurons and at synapses also do far more than generate ATP. Mitochondria buffer calcium, drive Reactive Oxygen Species (ROS) signaling, and influence cell survival. Using the *Drosophila melanogaster* neuromuscular junction (NMJ) as a model synapse, we found loss of MCI components impact distinct synaptic tissues in profoundly different ways. We found that MCI impairment causes coarse cytological abnormalities at both the pre- and postsynaptic NMJ. It also causes a large increase in mitochondrial superoxide/ROS. Important differences emerge upon examination of individual tissues. NMJ activity is dampened when MCI is impaired in the postsynaptic muscle. This is because muscle ROS disrupts the postsynaptic density and impairs efficient apposition of pre- and postsynaptic machinery. By contrast, in neurons, the presence of mitochondrial ROS signals an enhancement of presynaptic active zone material. This active zone enhancement appears to be homeostatic and responsible for keeping synaptic outputs strong. Interestingly, NMJ activity can be dampened when MCI is impaired in neurons – but this only happens when it is combined with other insults, like scavenging of ROS, loss of intracellular calcium homeostasis, or loss of glycolysis as an alternative energy source. We are using the *Drosophila* genetic toolkit to understand how loss of MCI causes profoundly divergent responses in distinct synaptic tissues.

Disclosures: B. Mallik: None. **C. Frank:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.01/B72

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: JSPS KAKENHI JP24H01497
JSPS KAKENHI JP23K21755
JSPS KAKENHI JP23K18485
JSPS KAKENHI JP22H05698
JSPS KAKENHI JP21H03606
JSPS KAKENHI JP23K28178
JSPS KAKENHI JP23K21713
JSPS KAKENHI JP23H03488
JSPS KAKENHI JP21H03532
JSPS KAKENHI JP21K06702
JSPS KAKENHI JP20H04341
JSPS KAKENHI JP24K18267
JSPS KAKENHI JP21K15247

Title: Quantitative description of the voltage-activated Ca^{2+} and K^+ currents responsible for the membrane response in Paramecium multimicronucleatum. I. Kinetic analysis of the K current

Authors: *T. TOMINAGA[1,2,3], Y. TOMINAGA[4];
[1]Tokushima Bunri Univ., Kagawa, Sanuki, Japan; [2]KAGAWA School of Pharmaceutical Sciences, Tokushima Bunri University, Sanuki, Japan; [3]Institute of Neuroscience, Tokushima Bunri University, Sanuki, Japan; [4]Inst. of Neurosci., Tokushima Bunri Univ., Sanuki, Japan

Abstract: A unicellular freshwater organism, *Paramecium*, has an oval spherical shape (250 µm long, 50 µm diameter) enclosed by a continuous surface membrane, including its 15000 surface-projected motile bodies (cilia). The membrane potential control of the behavior of *Paramecium* has been extensively studied since the late 1960s and was called a “swimming neuron”. The recent integrative approach has shed new light on this model animal cell. The large size of the paramecium cell allows precise voltage clamp (VC) experiments with two electrode configurations. Here, we used a newly designed amplifier system to achieve a time-limited VC application to minimize cell damage, we achieved fast (tau ~ 400 µs) VC.The membrane potential of *P. multinucleatum* was shifted from its resting level (-35mV) to different levels. At the beginning of a depolarizing voltage step, the membrane current reaches a level in the outward direction (initial current). From the level of the initial current, the membrane current decreased in an inward direction, reached its peak, and then changed direction in an outward direction (early transient current) until it reached a steady level in an outward direction (depolarization-activated late current). During hyperpolarizing steps, the initial current was inwardly directed. Over time, the membrane current gradually increased from the initial inward current to an outward current until it reached a level (hyperpolarization-activated late current). These current responses consisted of an early transient current carried by Ca2+, a depolarization- and the hyperpolarization-activated late current carried by K and a linear leak current with a reversal potential of -35 mV.In the present study, we chose to focus on the K^+ currents. A detailed analysis of the early Ca^{2+} inward current responsible for action potential generation is described

elsewhere.Since pharmacological suppression of the Paramecium Ca^{2+} channel is limited, we used a three-step voltage clamp strategy to isolate K^+ current. In the first 40 mV 30 ms depolarizing step (V1), the Ca^{2+} current was inactivated, and then the membrane voltage was changed to the second step (V2). The instantaneous current components were analyzed from the membrane current at the following voltage step (V3). The results show the two different K^+ conductances. We will show the Hodgkin-Huxley model of the currents. This will help to understand the prototype of intelligence controlled by membrane potential.

Disclosures: **T. Tominaga:** None. **Y. Tominaga:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.02/B73

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH-NINDS R01NS130759
NIH-NINDS R01NS105958

Title: Benchmarking the RxD module to implement intracellular signaling in complex Purkinje cell models

Authors: B. PAHLAVAN[1], Z. YANG[2], J. M. CHRISTIE[2], ***F. SANTAMARIA**[3];
[1]Neuroscience, Developmental and Regenerative Biol., Univ. of Texas at San Antonio, San Antonio, TX; [2]Physiol., Univ. of Colorado Sch. of Med., Aurora, CO; [3]Univ. of Texas at San Antonio, San Antonio, TX

Abstract: Modeling intracellular neuronal biochemical signaling is essential to investigate synaptic integration, coding, and plasticity. For example, the diffusion of calcium is important to link synaptic activity and the expression of long-term synaptic plasticity. In the NEURON simulation environment, NMODL files implement a simplified calcium diffusion by assuming a radial process approximated by concentric shells in each compartment. However, the recently developed RxD module provides the possibility to model 1D and 3D diffusion processes. Here, we present our initial work on modeling intracellular diffusion using the RxD module in a Purkinje cell model. We implement 3D diffusion in smooth thick dendrites, and 1D diffusion in spiny thin dendrites. In spiny dendrites, we implement active transport between cytosol and endoplasmic reticulum sub-compartments with SERCA pump as well as calcium-induced calcium release through IP3 receptors. The soma and smooth dendrites can also be modeled traditionally as radial diffusion between concentric shells. The 1D axial diffusion allows us to model the calcium flow between all compartmental sections and, most importantly, between the spiny dendrites and attached passive spines, which was not achievable in traditional NMODL files. The 1D diffusion can interact with full 3D or axial diffusion processes in soma and smooth dendrites. Furthermore, we present our initial efforts to implement the biochemical signaling

cascade involved in the expression of long-term depression in the parallel fiber-Purkinje cell synapses. In this case, we allow calcium diffusion from the dendrite but model the other biochemical reactions exclusively in the spine head. We address challenges to improve the RxD module regarding flexibility in compartment structure definitions and mixtures of initialization parameters across complex models. We also discuss the computational requirements, time to model setup, and simulation times when using different modeling strategies and model sizes.

Disclosures: **B. Pahlavan:** None. **Z. Yang:** None. **J.M. Christie:** None. **F. Santamaria:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.03/B74

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH MH046742-26

Title: Fast Timescale Calcium-Dependent Modulation of Ion Channel Voltage Sensitivity Influences Neuronal Activity Profiles

Authors: *Y. MONDAL[1], E. MARDER[2], R. L. CALABRESE[3];
[1]Brandeis Univ., Waltham, MA; [2]Biol., Brandeis Univ., WALTHAM, MA; [3]Emory Univ., Atlanta, GA.

Abstract: Neurons are terminally differentiated cells that can maintain specific activity profiles over their lifetimes despite facing a plethora of environmental changes. In this study, we develop a computational model focused on a specific type of homeostatic plasticity: intrinsic activity-dependent plasticity. This model simulates how neurons maintain a target activity profile by adjusting either their ion channel density or voltage sensitivity to regulate intracellular calcium levels. The former can be thought to occur on slow time scales because they involve protein synthesis, the latter can be thought to occur on fast time scales because they involve post translational modification that don't involve protein synthesis (e.g. phosphorylation). Although both types of activity-dependent adjustments have been observed across various settings, only adjustments via ion channel density have been previously modeled computationally using calcium-mediated activity-dependent mechanisms. In the model, we explore how fast time scale calcium-mediated adjustments to ion channel voltage sensitivities impact a neuron's activity profile by shifting their activation and inactivation curves. These findings demonstrate that fast time scale homeostatic modulations of voltage sensitivities can impact the types of homeostatic activity profiles a neuron settles to in different contexts. These results may be used to understand how activity-dependent homeostatic adjustments operating through multiple mechanisms may be used to control neuronal excitability.

Disclosures: **Y. Mondal:** None. **E. Marder:** None. **R.L. Calabrese:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.04/B75

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: CIHR PJT-159794

Title: H_2O_2-dependent gating of a non-selective cation channel is enhanced by prior ionotropic acetylcholine receptor activation in *Aplysia* neuroendocrine cells

Authors: *K. H. LEE[1], N. S. MAGOSKI[2];
[1]Dept. of Biomed. and Mol. Sci., Queen's Univ., Kingston, ON, Canada; [2]Dept. of Biomed. and Mol. Sci., Queens Univ., Kingston, ON, Canada

Abstract: Long lasting neuronal activity can be evoked by a brief input but maintained with tonic, inward conductance(s). The gating of the channel(s) is often regulated by changes in second messengers and/or membrane voltage. For example, the neuroendocrine bag cell neurons of the sea snail, *Aplysia*, exhibit an extended firing of action potentials called the afterdischarge, which leads to the secretion of a reproductive hormone, and is followed by an ~18-hr refractory period where only single action potentials can be elicited upon stimulation. The afterdischarge is initiated from a resting potential of ~-60 mV with the opening of a monovalent cation-selective, ionotropic acetylcholine receptor, and sustained between -40 and -30 mV by a voltage-dependent, non-selective cation channel. We previously found that this cation channel is gated by H_2O_2-mediated oxidation on the cytoplasmic face and that H_2O_2-induced bursting in bag cell neuron clusters is greatly augmented following a prior acetylcholine exposure. Thus we hypothesize that the acetylcholine receptor and cation channel interact to determine burst initiation and maintenance. Here, individual, cultured bag cell neurons from adults (hermaphrodite; 200-600g) under whole-cell voltage-clamp at -60 mV presented an ~-200 pA current to bath-applied 1 mM H_2O_2, which was enhanced to ~-300 pA with prior pressure-application of 1 mM acetylcholine. Similarly, at a depolarized voltage of -30 mV, where the cationic current is active during the afterdischarge, the control H_2O_2-induced current (~-150 pA) was smaller than the acetylcholine-exposed response (~-200 pA). For the converse experiment, acetylcholine was applied twice, separated by ~40 min, resulting in a ~50% run-down in the acetylcholine-evoked current. This run-down was attenuated to ~80% when H_2O_2 was bath-applied between acetylcholine ejections. In agreement with the duration of the refractory period, recovery of the cholinergic current under control conditions required at least 6 hrs (~90%) with full recovery by ~24 hrs (~110%) after the first acetylcholine ejection. We propose that either a direct oxidation of the receptor or, an H_2O_2-induced activation of the cation channel through an unidentified mechanism, rescues the run-down of the acetylcholine receptor. These findings suggest a feedback interaction between two distinct channels despite their gating being temporally and spatially removed.

Disclosures: **K.H. Lee:** None. **N.S. Magoski:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.05/B76

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: CIHR PJT-159794

Title: Reactive oxygen species and tyrosine phosphorylation interact to gate a non-selective cation channel in aplysia neuroendocrine cells

Authors: *E. M. ROBICHAUD[1], N. S. MAGOSKI[2];
[1]Biomed. and Mol. Sci., Queen's Univ., Kingston, ON, Canada; [2]Biomed. and Mol. Sci., Queens Univ., Kingston, ON, Canada

Abstract: In the hermaphroditic sea snail, Aplysia californica, the neuroendocrine bag cell neurons exhibit an extended afterdischarge to trigger egg-laying behaviour. The afterdischarge is associated with both a drop in phosphotyrosine levels and an increase in intracellular hydrogen peroxide (H_2O_2). The depolarizing drive necessary for prolonged firing is maintained in part by the opening of a voltage-dependent, non-selective cation channel. Single-channel recordings indicate that gating of the channel requires tyrosine dephosphorylation, while macroscopic current measurements show that H_2O_2 directly opens the channel. However, the possibility that tyrosine phosphorylation and H_2O_2 interact to regulate cation channel activity has yet to be explored. Here, we initially examined the relationship between H_2O_2 and tyrosine phosphorylation by treating the two bag cell neuron clusters within the isolated abdominal ganglion for 1 hr with 1 mM H_2O_2; subsequently, clusters were fixed, sectioned and immunostained for phosphotyrosine. Compared to control (H_2O), clusters exposed to H_2O_2 presented reduced phosphotyrosine immunolabelling. To directly test cation channel function, individual bag cell neurons were placed in primary culture and whole-cell voltage-clamped at -30 mV using a Cs^+-based intracellular saline and standard Na^+-based external saline. Bath-application of 1 mM H_2O_2 or the tyrosine kinase inhibitors, 100 μM genistein or 20 μM PP1 all elicited an inward current of hundreds of picoamps (pA) ~ 1-minute post-addition. Applying either tyrosine kinase inhibitor before H_2O_2 occluded the H_2O_2-induced current; H_2O_2 alone produced an average response of ~-100 pA whereas with a prior application of genistein or PP1, the response was 10-15 pA, suggesting that these compounds gate a common channel. Conversely, when PP1 was applied after H_2O_2, the PP1-induced current was also attenuated, i.e., PP1 alone produced an inward current of ~-1000 pA, whereas following H_2O_2 the PP1-induced current was ~-60 pA. These preliminary results suggest a relationship between H_2O_2 and phosphotyrosine levels and cation channel gating. This work will provide the foundational research necessary to elucidate our understanding of the mechanisms underlying the regulation

of this cation channel, as well as the relationship between reactive oxygen species and tyrosine phosphorylation as it pertains to long-term changes to excitability.

Disclosures: E.M. Robichaud: None. **N.S. Magoski:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

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Program #/Poster #: PSTR009.06/B77

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH Grant R01NS115209

Title: Role of chloride dynamics in generation of bursting activity by the cold-nociception neurons in Drosophila larva

Authors: S. M. KOROGOD, *A. SAKURAI, N. MAKSYMCHUK, D. N. COX, G. S. CYMBALYUK;
Georgia State Univ., Atlanta, GA

Abstract: In *Drosophila* larvae, Class III (CIII) primary sensory neurons detect nociceptive cold temperatures. About half of these neurons report a fast temperature drop with transient bursting. How this bursting is generated remains unknown. Ca^{2+}-activated Cl^- current (I_{CaCl}) and dynamics of Cl^- concentration are implicated in this process [1]. Here, we use electrophysiological experiments and modeling to investigate the role of the Cl^- dynamics in mechanisms underlying pattern generation under a fixed temperature to delineate them from thermosensitive mechanisms.

In normal saline, 84% of the recorded cells exhibited spontaneous spiking activity at an average rate of 0.24 spikes/s. Among these, 59% displayed bursting and 31% showed bursts that accounted for more than half of all spikes ($Burst_{50}$). Low-Cl^- saline increased the average spike rate to 0.99 spikes/s, with 84% of cells exhibiting bursting, and in 60% of them with $Burst_{50}$. In normal saline, 35% of the cells showed only tonic spikes. 69% of these exhibited bursting in low- Cl^- saline. 15% of the cells were initially silent and then 86% of them generated bursting in low- Cl^- saline. The total spike rate exhibited a direct correlation with lowered Cl^- content. However, the percentage of spikes within bursts did not show a linear progression.

We upgraded the model [2], that describes bursting of CIII neurons in response to temperature drop, by including dynamics of concentrations of Cl^-, Na^+, and K^+. We included I_{CaCl}, background voltage-dependent Cl- current (CIC-2 type) $I_{ClC\text{-}2}$, Na^+/K^+ pump, Na^+ and K^+ leak currents, and K^+-Cl^- and Na^+-K^+-$2Cl^-$ co-transporters creating Cl^- outflux (F_{kcc}) and influx (F_{nkcc}). We investigated the shift of Cl^- reversal potential (E_{Cl}) and changes of patterns caused by a drop in extracellular Cl^- and by variation of F_{kcc} and F_{nkcc}. We also considered a simplified model with an *effective* leak current including Cl^- currents lumped together with Na^+ and K^+ leak currents, eliminating dynamics of Cl^- currents. We map oscillatory and silent regimes under effective

variation of E_{eLeak} and g_{eLeak}. We found large domains of silent and tonically-spiking regimes at low and high $E_{eLeak,}$ respectively, and a domain of bursting in an intermediate range of both parameters. We found that in a certain range of g_{eLeak} as E_{eLeak} grows the model transitions from silence to bursting and then from bursting to spiking.
Results of the electrophysiological experiments and the modeling show that the dynamics of Cl^- concentration modulate pattern generating mechanisms and promote bursting activity under certain conditions.

References

1. Himmel et al (2023) Elife. 2023 12:e768632
2. Maksymchuk et al (2023) IJMS 24:14638

Disclosures: S.M. Korogod: None. **A. Sakurai:** None. **N. Maksymchuk:** None. **D.N. Cox:** None. **G.S. Cymbalyuk:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.07/B78

Topic: B.06. Intrinsic Membrane Properties and Signal integration

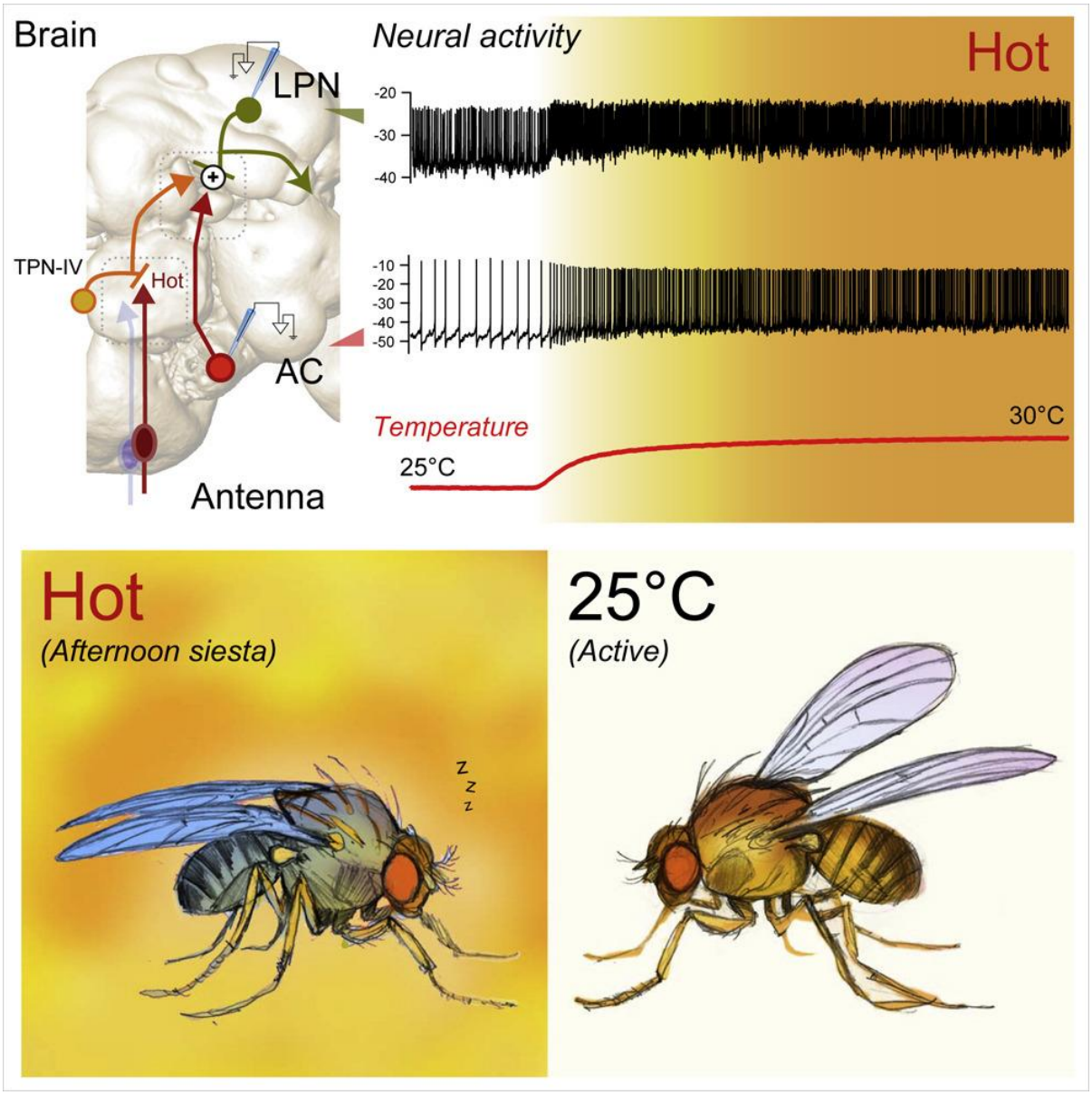
Support: US National Science Foundation DMS-2235451
Simons Foundation MP-TMPS-00005320 via the National Institute for Theory and Mathematics in Biology (NITMB)
NIH Grant R01NS086859

Title: Cellular and molecular properties of a hot-sensing circuit in Drosophila

Authors: *M. H. ALPERT[1,3], N. DING[2,3], W. L. KATH[2,3], M. GALLIO[1,3];
[1]Neurobio., [2]Engin. Sci. and Applied Mathematics, Northwestern Univ., Evanston, IL; [3]Natl. Inst. for Theory and Mathematics in Biol., Chicago, IL

Abstract: Small poikilotherms such as the fruit fly, *Drosophila*, depend on absolute temperature measurements to identify external conditions that are above (hot) or below (cold) their preferred range and to react accordingly. Hot and cold temperatures have a different impact on fly activity and sleep, but the circuits and mechanisms that adjust behavior to specific thermal conditions are not well understood. We have used patch-clamp electrophysiology to show that internal thermosensory neurons located within the fly head capsule (the AC neurons) function as a thermometer active in the hot range**.** AC neurons exhibit sustained firing rates that scale with absolute temperature – but only for temperatures above the fly's preferred ~25°C (i.e. "hot" temperature). We identify ACs in the fly brain connectome and demonstrate that they target a single class of circadian neurons, the LPNs. LPNs receive excitatory drive from ACs and respond robustly to hot stimuli, and we show that silencing ACs or LPNs blocks the restructuring of daytime "siesta" sleep which normally occurs in response to persistent heat.

To better understand the molecular mechanism of thermosensation in ACs, we performed Patch-seq on ACs and compared the results to patch-seq of other cells of the thermosensory system. Informed by gene expression analysis, our goal is to develop a morphologically realistic neuron model of ACs (based on EM connectome), populate this model with ion channels and candidate regulators based on their transcriptomic profile, and use an evolutionary algorithm to fit electrophysiological parameters measured in vivo.
Overall, we expect that our model will bring clarity on the ion channels, receptors, modulators (etc.) that are the key determinants of thermosensory responses in ACs.



Disclosures: **M.H. Alpert:** None. **N. Ding:** None. **W.L. Kath:** None. **M. Gallio:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.08/B79

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH Grant 1R01NS131457-01

Title: Sensory stimuli control C. elegans arousal via a defined set of integrator neurons that have diverse temporal properties

Authors: *A. KUNDRA[1], S. W. FLAVELL[1], S. N. BASKOYLU[2], E. BUENO[1], S. PUGLIESE[1];
[2]Neurosci., [1]MIT, Cambridge, MA

Abstract: Transient sensory stimuli can trigger long-lasting changes in behavior and cognition. For example, repeated aversive experiences can trigger persistent, long lasting changes in arousal, mood and cognitive flexibility. These lasting changes in behavior allow animals to adaptively respond to the environment, but can also drive maladaptive behavioral responses in psychiatric diseases such as depression. The neural mechanisms by which transient sensory stimuli trigger persistent changes in neural activity and behavior remain poorly understood. Here, we examine these mechanisms in the simple nervous system of the roundworm C. elegans. Using a combination of whole-brain neuronal imaging and optogenetics, we study how C. elegans accumulates evidence of past aversive experiences in both artificially and naturally aversive environments. We used a whole-brain imaging approach in a naturally aversive environment to identify a set of neurons that integrate aversive sensory stimuli. We next tested the identified neurons in optogenetic experiments, by activating blue light sensitive channelrhodopsins expressed under cell specific promoters. We used behavioral outputs to confirm that these neurons integrate aversive sensory stimuli over different timescales, ranging from seconds to minutes. We further explored functional connections between pairs of integrator neurons, organizing them in a functionally hierarchical network. We find that two parallel paths generate arousal over short and long timescales respectively, allowing the animals to respond to both the quantity and recency of aversive stimuli.We propose that changes in brain-wide arousal states are controlled via persistent activity in a set of defined neurons that integrate sensory information and impact behavior over diverse timescales.

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Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: Wellcome Senior Research Fellowship (214352/Z/18/Z)
Sainsbury Wellcome Centre Core Grant (219627/Z/19/Z)
Sainsbury Wellcome Centre Core Grant (GAT3755)
A*STAR National Science Scholarship

Title: Input-output transformation in dorsal periaqueductal gray neurons during escape behaviour

Authors: *Y. TAN[1], D. CAMPAGNER[1], A. THAMILMARAN[2], S. LIU[2], N. ZERNICKA-GLOVER[2], T. BRANCO[1];
[1]Sainsbury Wellcome Ctr., London, United Kingdom; [2]Univ. Col. London, London, United Kingdom

Abstract: Escape is a stereotyped but flexible behaviour sensitive to many intrinsic and extrinsic factors, such as competing motivations and resources. Escape initiation is controlled by glutamatergic neurons in the dorsal periaqueductal gray (dPAG), which receive inputs from a multitude of areas that signal rich information beyond the threat stimulus. Synaptic integration of these convergent inputs by dPAG neurons therefore likely determines whether the animal escapes from threat. Here we aimed to measure the input-output function of dPAG neurons to understand how presynaptic input from different sources is processed to control action potential firing and escape initiation. We started by studying the integrative properties of dPAG dendrites using both dual somatic and dendritic whole-cell recordings of proximal dendrites and holographic ChR2 stimulation of distal dendrites in vitro, which suggested that dPAG neurons are highly electrotonically compact despite their long dendrites. To investigate how this property might influence the generation of spikes in the network during physiological spatiotemporal patterns of inputs that evolve during escape, we first generated a subcellular map of synapses onto the dPAG dendritic tree from 5 different input areas, by combining optical clearing, viral labelling and confocal imaging to reconstruct individual dPAG neurons and their synapses. We found that inputs from the superior colliculus (SC), inferior colliculus (IC) and ventromedial hypothalamus (VMH) are randomly distributed across the dendritic tree, while inputs from the anterior cingulate cortex (ACC) and dorsal premamillary nucleus (PMd) are enriched proximally. We then simultaneously followed the activity profile of neurons in dPAG and its presynaptic partners over the course of escape behaviour under various conditions, using multi-probe chronic Neuropixels implants combined with cell type-specific and projection-specific opto-tagging. We are currently using the biophysical, anatomical and in vivo spike data to generate models of PAG neurons that predict action potential output from presynaptic spike trains and provide a mechanistic description of how different input streams are integrated in dPAG neurons to control escape initiation.

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Poster

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Program #/Poster #: PSTR009.10/B81

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: 5R01AA028861-03

Title: Changes in intrinsic excitability in a population of withdrawal- activated neurons in the medial prefrontal cortex of alcohol self-administering mice

Authors: *S. RODRIGUEZ[1], J. T. O'BRIEN[2], S. KROENER[3];
[1]Neurosci., Univ. of Texas Dallas, Plano, TX; [2]Neurosci., Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [3]Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas Sch. of Behavioral and Brain Sci., Richardson, TX

Abstract: Alcohol use disorder (AUD) is linked to impairments of the prefrontal cortex (PFC) that compromise cognitive and executive functions, leading to heightened risk of relapse. In rodent models, activation of the prelimbic (PL) or infralimbic (IL) regions of the PFC are thought to promote alcohol intake or aid the extinction of drug memories, respectively. However, even within these regions, neurons may show heterogeneous responses to alcohol (EtOH) or other reinforcers. Using a transgenic mouse line (TRAP2/Ai9) which permits fluorescent tagging of active populations, we identified PL and IL neurons that were active during withdrawal in mice that self-administered either alcohol or sucrose in daily operant sessions. We conducted whole-cell patch-clamp current-clamp recordings in PL and IL neurons that were either active (Ai9+) or inactive (Ai9-) following an 18-hour withdrawal. While overall response rates for sucrose were significantly higher over 3 weeks of self-administration, mice in the EtOH group showed similar relative response rates during a cue-induced reinstatement session, following 5 days of extinction, suggesting the reinforcing properties of EtOH. Neurons in both regions of the mPFC from EtOH self-administering mice showed increased excitability compared to neurons from sucrose-drinking mice. In the IL withdrawal-activated Ai9+ neurons showed increased rates of action potential firing in alcohol mice, while there were no differences in the intrinsic excitability of Ai9- cells from sucrose and alcohol self-administering mice. In the PL Ai9+ cells from alcohol-exposed mice showed increased action potential, whereas Ai9- neurons showed no difference in firing rates between groups, suggesting differential, substance-specific modulation of neuronal excitability in the PL region. Increased neuronal excitability is reflected in lower rheobase currents and AHP amplitude in Ai9+ cells of EtOH mice. Acute application of 20mM alcohol decreased neuronal activity in Ai9+ neurons, but had no effect on Ai9- neurons in both the PL and IL cortices. Overall, our results highlight a potential withdrawal neuron population in the mPFC and they support the existence of a PL/IL dichotomy in the context of reward-seeking. Ongoing experiments are identifying the role of withdrawal neurons in cue-induced reinstatement using immunohistochemistry. These findings underscore the need for further research to elucidate the specific neurophysiological mechanisms underlying alcohol withdrawal, which may pave the way for more targeted therapeutic interventions for AUD.

Disclosures: S. Rodriguez: None. **J.T. O'Brien:** None. **S. Kroener:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

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Program #/Poster #: PSTR009.11/B82

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH F31MH127910-03
NIH R01NS115543 05

Title: Activity-dependent changes in Npas4+ neurons during fear learning in the lateral amygdala

Authors: *C. RAMOS[1], P. E. CASTILLO[2];
[1]Albert Einstein Col. of Med., Brooklyn, NY; [2]Dominick P Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: The activation of immediate early genes (IEGs) has been used to identify neurons constituting a NE during a learning task. Expression of specific IEGs varies depending on the task performed, suggesting specificity according to cognitive process and brain region. Recent work has shown that multiple IEGs can be activated during a task to respectively recruit distinct populations of cells, comprising a heterogenous ensemble of activated neurons for a given experience. It is unknown, however, how activated neurons of specific IEGs distinctly contribute to learning. The transcription factor IEG Npas4 is activated in an ensemble of neurons in the lateral amygdala (LA) during auditory fear learning, in which a neutral auditory stimulus is accompanied by and subsequently linked to an aversive experience. Loss of Npas4 in the LA impairs fear learning, suggesting that distinct changes in LA neurons expressing Npas4 are essential for facilitating fear learning. This distinct link between expression of an IEG and a behavior provides a unique opportunity to identify specific mechanisms of plasticity impacting a local circuit during a learning process. We hypothesize that distinct activity-dependent changes occur selectively in Npas4+ cells, modifying the LA circuit to facilitate fear learning. Leveraging the Npas4-specific Robust Activity Marker (NRAM) to identify Npas4+ cells during fear learning, we assessed changes in Npas4+ cells to determine the effects of fear learning on LA circuitry and function. We determined that fear learning activates Npas4 in both excitatory and inhibitory neurons in the LA. In studying the changes of the Npas4-activated excitatory population in the LA, we found that Npas4+ excitatory neurons display changes in excitability, but not in excitatory or synaptic transmission. Our results thus far characterize the functional characteristics of Npas4+ neurons after fear learning.

Disclosures: C. Ramos: None. **P.E. Castillo:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

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Program #/Poster #: PSTR009.12/B83

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH Grant MH131570
NIH Grant MH120136

Title: Dynamic integration of corticothalamic inputs in projection-defined neurons of the paraventricular nucleus of the thalamus.

Authors: *D. JALLOUL[1,2], G. AQUINO-MIRANDA[1], F. H. DO MONTE[1,2], M. BEIERLEIN[1,2];
[1]McGovern Med. Sch. at UTHealth, Houston, TX; [2]The University of Texas MD Anderson Cancer Center UTHealth Houston Graduate School of Biomedical Sciences, Houston, TX

Abstract: Neuronal activity in corticothalamic (CT) afferents is crucial for controlling the excitability of thalamic neurons across different time scales. Prior research has focused extensively on the functional organization of CT circuits contacting sensorimotor thalamic nuclei, but our understanding of how CT circuits control activity in the limbic thalamus remains incomplete. The paraventricular nucleus of the thalamus (PVT) is a key structure of the limbic thalamus and is involved in processing both cognitive and emotional information. PVT contains neurons with diverse molecular and physiological properties, as well as distinct synaptic connectivity to downstream targets. PVT neurons receive dense inputs from prelimbic (PL) cortical areas, which convey information relevant to decision-making and goal-oriented behavior via two functionally distinct pathways: direct monosynaptic excitatory inputs and indirect disynaptic projections via the anteroventral thalamic reticular nucleus (avTRN) that mediates feed-forward inhibition. How distinct types of target-defined PVT neurons integrate PL and avTRN inputs to generate behaviorally relevant outputs remains poorly understood. Here, we employed neuronal tracing, optogenetics and whole-cell recordings in rat brain slices to characterize PL and avTRN inputs onto PVT neurons that project to the nucleus accumbens (PVT-NAc) or the central amygdala (PVT-CeA), two largely non-overlapping subpopulations of PVT neurons that bidirectionally regulate motivational and emotional responses. We found that the ability of PVT neurons to maintain action potential output during sustained depolarizations varied according to their projection targets. While most PVT-CeA neurons exhibited a rapid decay of action potential amplitudes and entered into prominent depolarization block, PVT-NAc neurons maintained their firing under the same conditions. Next, we used a viral approach and optogenetics to reveal the temporal dynamics of synaptic inputs to PVT. Photoactivation of PL afferents with brief stimulus trains led to large amplitude postsynaptic responses that displayed short-term facilitation over a range of frequencies in both subpopulations of PVT neurons. Interestingly, photoactivation of avTRN inputs with brief trains led to sustained responses in PVT-NAc neurons, but more transient responses in PVT-CeA neurons resulting in short-term depression. Taken together, our findings suggest that synaptic short-term dynamics and intrinsic properties interact to generate distinct neuronal activity in PVT subpopulations, thereby contributing to their unique roles in mediating behavioral responses.

Disclosures: **D. Jalloul:** None. **G. Aquino-Miranda:** None. **F.H. Do Monte:** None. **M. Beierlein:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.13/B84

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NINDS K08 NS094643
NIMH R56 MH122810
NIMH R01 MH131857

Title: Differences in HCN channel function between medial and lateral mediodorsal thalamus drive functional differences in neurophysiological properties

Authors: *G. J. HECKLER[1], G. J. ORDEMANN[2], A. C. BRUMBACK[3];
[1]Neurol., The Univ. of Texas at Austin, Austin, TX; [2]Neurol., UT Austin, Austin, TX;
[3]Neurology, Pediatrics, Neurosci. and The Ctr. for Learning and Memory, Ctr. For Learning & Memory, Univ. of Texas, Austin, Austin, TX

Abstract: Title: Differences in HCN channel function between medial and lateral mediodorsal thalamus drive functional differences in neurophysiological properties
Gregory J. Ordemann, Griffin Heckler, Audrey C. Brumback
The mediodorsal thalamus (MD) is a thalamic subregion involved in higher order processes such as working memory, decision making, and cognitive control. Strong reciprocal connectivity between MD and the medial prefrontal cortex (mPFC) supports higher order cognition. Investigations of mPFC connectivity with MD have shown the importance of theta and beta rhythmic activity in MD to working memory. Subthreshold properties imparted by Hyperpolarization Activated Cyclic Nucleotide Gated (HCN) channels contribute to the ability of neurons to amplify signals of specific frequency ranges. Our lab recently identified a difference in HCN channel activity between the medial (MD-M) and lateral (MD-L) subnuclei in MD. Here, we used a combination of histological techniques and patch clamp electrophysiology to determine the molecular substrates for differences in HCN subunit activity between MD-M and MD-L. Using pharmacology in conjunction with electrophysiological recordings, we test how differential HCN channel properties influence temporal integration in MD-M and MD-L subnuclei. Our findings bolster previous research suggesting unique contributions of MD subnuclei to complex behaviors and further implicate differences in HCN activity as a source of circuit-level specialization in transthalamic signaling in the prefrontal network.

Disclosures: **G.J. Heckler:** None. **G.J. Ordemann:** None. **A.C. Brumback:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

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Program #/Poster #: PSTR009.14/B85

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NINDS K08 NS094643
NIMH R56 MH 122810
NIMH R01 MH131857

Title: Electrophysiological characterization of mediodorsal thalamocortical neurons in a mouse model of fragile X syndrome

Authors: *G. ORDEMANN[1], A. KIZIMENKO[2], G. HECKLER[3], A. C. BRUMBACK[4]; [1]UT Austin, Austin, TX; [2]Neurol., Univ. of Texas At Austin, Austin, TX; [3]Univ. of Texas at Austin, Austin, TX; [4]Neurology, Pediatrics, Neurosci. and The Ctr. for Learning and Memory, Ctr. For Learning & Memory, Univ. of Texas, Austin, Austin, TX

Abstract: Fragile X syndrome (FXS) is a neurodevelopmental disorder associated with intellectual disability and autism spectrum disorder. FXS occurs through hypermethylation of the *FMR1* gene on the long arm of the X-chromosome, which results in a lack of the protein product of the gene, FMRP. FMRP modulates the expression and function of a wide variety of proteins, including voltage-gated ion channels such as Hyperpolarization-Activated Cyclic Nucleotide gated (HCN) channels. Our lab recently identified that relatively increased HCN channel activity in lateral MD (MD-L) compared to medial MD (MD-M) causes MD-L neurons to have relatively shorter membrane time constants, lower input resistance, and higher rheobase. Here, using a combination of retrograde labeling and *ex vivo* whole cell electrophysiology in mice, we investigated how a lack of *Fmr1* affects intrinsic cellular properties in MD subnuclei with a specific focus on HCN channel activity. We found that in MD-L neurons, *Fmr1* knockout caused a decrease in HCN-mediated membrane properties such as voltage sag. These changes in subthreshold properties were accompanied by changes in suprathreshold neuron properties such as the variability of action potential timing.

Disclosures: G. Ordemann: None. **A. Kizimenko:** None. **G. Heckler:** None. **A.C. Brumback:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

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Program #/Poster #: PSTR009.15/B86

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH EY017836-16 (JHS)
NINDS intramural research program (JSD).

Title: Characterization of a polyaxonal amacrine cell in the mouse retina

Authors: *M. A. MUSGROVE[1,2], J. H. SINGER[1], J. S. DIAMOND[3];
[1]Biol., Univ. of Maryland, Col. Park, College Park, MD; [2]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD; [3]Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD

Abstract: The mammalian retina is a well-studied, laminar structure that is isolated from the rest of the central nervous system. It is composed of the following neuronal types: photoreceptors, bipolar cells, amacrine cells (AC), horizontal cells, and the retinal ganglion cells. Inhibition provided by ~ 60 different ACs subtypes has an imperative role in the diverse computational output of the retina. ACs originally received their name due to the perceived lack of an axon; however, there are many ACs that have multiple, long axons. These cells are referred to as the polyaxonal ACs and are varied in morphology across cell types. Recently, we identified a polyaxonal AC, the nNOS (neuronal nitric oxide synthase)-1 AC, to be a significant component of the rod bipolar pathway in the mouse retina. The nNOS-1 AC has multiple axons that branch off of different dendrites. Here, we address the question of whether these axons can operate independently of one another. By recording action potentials from nNOS-1 AC somas, we found electrophysiological evidence for multiple, independent action potential initiation sites across the neuronal morphology. Through immunohistochemistry, we have found known axon initial segment markers at each of the axons within the nNOS-1 AC. Calcium imaging experiments paired with whole cell recordings have confirmed a single action potential can propagate down one axon without propagating down the others. This would provide evidence for multiplexed processing of synaptic inputs. In summary, our investigation of the nNOS-1 AC will help us to understand the function of an under-studied set of neurons that mediate long-range inhibition in the mammalian retina. Additionally, our findings in the nNOS-1 AC provide a functional blueprint of a cell that offers insight to unique biophysical adaptations of neurons.

Disclosures: M.A. Musgrove: None. **J.H. Singer:** None. **J.S. Diamond:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

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Program #/Poster #: PSTR009.16/B87

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: Brains and Behavior Fellowship from the Neuroscience Institute of Georgia State University

Title: Polyglot entrainment for higher dimensional neuronal dynamic models

Authors: *L. A. WIJAYASOORIYA[1], R. QASIM[2], E. KHAN[2], P. SANAEI[1];
[1]Dept. of Mathematics and Statistics, Georgia State Univ., Atlanta, GA; [2]Inst. of Numerical Sci., Kohat Univ. of Sci. & Technol., Kohat, Pakistan

Abstract: The entrainment of biological oscillators is a classic problem in the field of dynamical systems and synchronization. We explore a novel type of entrainment mechanism referred to as polyglot entrainment (multiple disconnected 1:1 regions) for higher dimensional nonlinear systems. Polyglot entrainment has been recently explored only in two-dimensional slow-fast models in the vicinity of Hopf bifurcations. Heading towards generality, in this study, we investigate the phenomenon of polyglot entrainment in higher-dimensional conductance-based models including the four-dimensional Hodgkin-Huxley model and its reduced three-dimensional version. We utilize dynamical systems tools to uncover the mechanism of entrainment and geometric structure of the null surfaces to explore the conditions for the existence of polyglot entrainment in these models. In light of our findings, in the vicinity of HB, when an unforced system acts as a damped oscillator and the fixed point is located near a cubic-like manifold, polyglot entrainment is observed.

Disclosures: L.A. Wijayasooriya: None. **R. Qasim:** None. **E. Khan:** None. **P. Sanaei:** None.

Poster

PSTR009: Intrinsic Properties: Diversity and Function

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.17/B88

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NSF Grant Neuronex 2015276

Title: Gradients of pyramidal neuron properties near the top of the primate cortex hierarchy

Authors: *G. GONZALEZ-BURGOS[1], T. MIYAMAE[1], Y. NISHIHATA[2], O. A. KRIMER[1], H. SON[1], K. GURNSEY[1], D. A. LEWIS[1];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Nara Med. Univ., Nara, Japan

Abstract: In primates, the dorsolateral prefrontal (DLPFC) and posterior parietal (PPC) cortices are key nodes positioned near the top of the hierarchy in the network of areas mediating working memory and attention. We reported previously (JNeurosci 39:7277, 2019) that despite sharing many similar features with the PPC, such as cytoarchitectonics and connectivity, the DLPFC from rhesus macaques contains layer 3 pyramidal neurons (L3PNs) with greater electrophysiological diversity, larger basal dendrites and higher dendritic spine density relative to PPC L3PNs.
Here we report data from ongoing experiments seeking to confirm and expand our previous findings of greater electrophysiological diversity in DLPFC, and to assess if DLPFC-PPC differences in L3PN dendrites correlate with: 1) excitatory synapse strength, 2) intrinsic electrophysiology and 3) the response observed in single L3PNs during episodes of sustained

network activity. In acute slices from macaque DLPFC and PPC, voltage clamp is used to record spontaneous EPSCs (sEPSCs) and assess excitatory synaptic strength, and is combined with current clamp recordings to characterize membrane properties. During the last phase of recording, the artificial cerebro-spinal fluid (ACSF) is replaced by the modified ACSF introduced by Sanchez Vives and McCormick (Nat Neurosci 3:1027, 2000), designed to generate episodes of enhanced network activity. All L3PNs are filled with biocytin, stained and reconstructed to assess the associations between neuronal morphology and the electrophysiology of each cell.
Our ongoing analysis shows that DLPFC L3PNs displayed regular spiking (RS) or bursting (B) electrophysiological phenotypes (DLPFC, RS: n=17/28; B: n=11/28, the latter including 2 strong oscillatory bursting L3PNs). In contrast, the majority of PPC L3PNs had RS properties and only a small subset of the PPC L3PNs were B cells (PPC, RS: 25/27; B: 2/27; strong oscillatory bursting not observed). These data both confirm and extend our previous findings (JNeurosci 2019) by showing the presence of strong oscillatory bursting neurons in DLPFC.
Interestingly, preliminary assessment of the activity recorded during application of the Sanchez-Vives 2000 ACSF showed that, among a diversity of responses which included a near absence of changes in membrane potential, single DLPFC L3PNs appeared more likely than PPC L3PNs to display persistent depolarization episodes often accompanied by relatively low frequency spiking. Moreover, our current analysis suggests that persistent depolarization is more frequently observed in RS than B neurons, particularly those with strong oscillatory bursting intrinsic properties.

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Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

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Program #/Poster #: PSTR009.18/B89

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: Marie Skłodowska-Curie grant agreement No 956414

Title: Exploring Signal Processing Compartmentalization in the Cerebellar Circuit using a High-Density Multielectrode Array

Authors: *Y. LI[1], F. MAINARDI[2], L. MAPELLI[3], E. D'ANGELO[4];
[1]Dept. of Brain and Behavioral Sci., Unverisity of Pavia, PAVIA, Italy; [2]Unverisity of Pavia, Pavia, Italy; [3]Dept of Brain and Behavioral Sci., [4]Brain and Behavioral Sci., Univ. of Pavia, Pavia, Italy

Abstract: Over the past few decades, extensive efforts were devoted to elucidate the different roles of the cerebellum, extending it beyond the traditional role in motor control. In particular,

the latest investigations have emphasized cerebellar involvement in emotional and social functions. Interestingly, anatomical and functional evidence guided the identification and characterization of functional subdivisions within the cerebellum. For example, the diverse cerebellar cell types vary in density, size, and morphology between the cerebellar vermis and hemisphere, between the anterior and posterior lobules, as well as between different locations within the same folia (crown/apex). Functional investigations also in humans revealed a certain degree of compartmentalization, with lobules involved in specific functions and more integrative ones. The cellular and network variations described in the cortical circuit in different lobules might provide an explanation for regional circuits devoted to specialized functions, such as motor and cognitive processes. In the specific context of emotional and social functions, the cerebellar involvement seems to be limited to specific regions, such as lobules VI in the vermis and Crus I in the hemispheres. Despite the increasing knowledge about the heterogeneity and complexity of neuronal populations, the relationship with cerebellar functions is still unclear. Herein, we employed High-Density Multielectrode Arrays (HD-MEAs) in mouse acute cerebellar slices to investigate cortical connectivity and information processing in different lobules. Our preliminary results indicate that the mean firing rates of Purkinje cells vary across different lobules in the cerebellar cortex. In particular, the central lobules exhibit higher Purkinje cell firing rates compared to the posterior cerebellum. Local inhibition is also a key factor determining circuit physiology in the cerebellar cortex. The inhibitory transmission blockade revealed the role of local inhibition in Purkinje cell spontaneous activity. Our preliminary data also suggests that this modulation could be region dependent. Furthermore, we stimulated mossy fibers to activate the cortical network in three different lobules (III, VI, and VIII), potentially involved in different functions, to characterize the responses of the main neuronal types to different activity ranges. This experimental setting is expected to reveal the possible regional difference in cerebellar network activity and whether local inhibition plays a role in determining these differences.

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Poster

PSTR009: Intrinsic Properties: Diversity and Function

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Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH 1UG3NS123958-01
NIH Diversity Supplement 3UG3NS123958-01S1
Research Endowment Fund of the Department of Anesthesiology and Critical Care Medicine

Title: Machine Learning Elucidates Neuronal Properties that Determine Multi-Firing in Human and Mouse Dorsal Root Ganglion Neurons

Authors: *N. ZUREK[1], S. THIYAGARAJAN[1], R. EHSANIAN[1], A. GOINS[1], S. GOYAL[1], C. G. LAMBERT[2], K. N. WESTLUND HIGH[1], S. R. A. ALLES[1];
[1]Anesthesiol. and Critical Care Med., Univ. of New Mexico Sch. of Med., Albuquerque, NM; [2]Intrnl. Med., Univ. of New Mexico, Dept. of Intrnl. Med., Div. of Translational Informatics, Albuquerque, NM

Abstract: Human and mouse dorsal root ganglia (hDRG and mDRG) neurons are important tools in understanding the molecular and electrophysiological mechanisms that underlie nociception and drive pain behaviors. Within the DRG there are several neuronal subtypes and these neurons exhibit a variety of firing patterns. One of the simplest differences in firing phenotypes is that neurons are single-firing (exhibit only one action potential) or multi-firing (exhibit 2 or more action potentials). To determine if single- and multi-firing hDRG exhibit differences in intrinsic properties, firing phenotypes, and AP waveform properties, and if these properties could be used to predict multi-firing, we measured 22 electrophysiological properties by whole-cell patch-clamp electrophysiology of 94 hDRG neurons from 6 male and 4 female human donors. We then analyzed the data using several machine learning models to determine if these properties could be used to predict multi-firing. We used 1000 iterations of Monte Carlo Cross Validation to split the data into different train and test sets and tested the Logistic Regression, k-Nearest Neighbors, Random Forest, Supported Vector Classification, and XGBoost machine learning models. All models tested had a greater than 80% accuracy on average, with Supported Vector Classification and XG Boost performing the best. We found that several properties correlated with multi-firing hDRG neurons and together could be used to predict multi-firing neurons in hDRG including a long decay time, a low rheobase, and long first spike latency. We next trained the models using all 94 hDRG recordings and used 20 mDRG recordings as a test set to see if the same models were predictive in both species. We found that the hDRG models were able to predict multi-firing with 90% accuracy in mDRG. Since multi-firing neurons are more excitable than single-firing neurons and neuronal hyperexcitability is a hallmark of chronic pain, targeting the neuronal properties that lead to multi-firing could elucidate better targets for treatment of chronic pain such as peripheral neuropathy.

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Poster

PSTR009: Intrinsic Properties: Diversity and Function

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.20/B91

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Title: Investigation of Piezo Receptors Involved in the Regulation of RhoA Pathway in Neurons

Authors: *S. SIMSEK[1], G. OZTURK[2];
[1]Neurosci., Istanbul Medipol Univ. - SABITA, Istanbul, Turkey; [2]Physiol., Istanbul Medipol Univ., Istanbul, Turkey

Abstract: The Rho GTPase family signaling pathway has important roles in a variety of neuronal functions, from cell migration to survival and from axonal guidance to regeneration. Piezo receptors on the cell membrane, which have become popular recently, are ion channels that respond to mechanical force and play an important role in cell behavior. The dorsal root ganglion (DRG) neurons in the peripheral nervous system express Piezo2. It is thought that Piezo2 channels activate RhoA protein signaling pathway in peripheral neurons against nerve injuries such as the axotomy which is a model of axonal damaged induced in the neurons in vitro. It seems likely that Piezo2 channels expressed by neurons are associated with the RhoA protein signaling pathway. The subject of this research is to investigate the RhoA activation in DRG neurons in vitro cell culture in axon extension and retraction processes and in their response to axon injury and to investigate its relationship with Piezo2 channels. It is known that the RhoA signaling pathway is activated after axon injury, as a result of the phosphorylation of downstream effectors, the cell soma of neurons shrinks and retracts their axons. It has been investigated that mechanical stimulation of Piezo2 channels in DRG neurons triggers cell shrinkage and triggers an increase in intracellular Ca^{+2} ion. Using RhoA inhibitor, it has been confirmed that Piezo channels induce cell contraction through RhoA. Within the scope of this research, it was concluded that the RhoA signaling pathway triggers cell shrinkage and contraction in neurons after axotomy and that they do through Piezo2 receptors, which are the strongest candidates for mechanoreceptors.

Disclosures: S. Simsek: None. **G. Ozturk:** None.

Poster

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Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH grant R01DK129194

Title: Effects of kHz-frequency electric field stimulation (kHz-FS) on neurons and glial cells in dorsal horn of the spinal cord

Authors: *S. KARNUP[1], T. KAMIJO[2], S. L. DAUGHERTY[1], J. BECKEL[1], N. YOSHIMURA[3];
[1]Pharmacol. and Chem. Biol., Univ. of Pittsburgh, Pittsburgh, PA; [2]Pharmacol. and Chem. Biol., [3]Dept Urology, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

Abstract: Nociceptive signaling arrives to the dorsal spinal cord and is processed in laminae I/II/III. Neurons of the dorsal horn are not the only elements providing this processing. Glial

cells remove excess of K^+ from the extracellular space preventing uncontrolled overexcitation or seizures. Clinically accepted spinal cord stimulation for chronic pain treatment utilizes electric currents of 10 kHz frequency. The mechanism of action of this treatment is still unknown. In this work we compared responses of unidentified neurons and glial cells in lamina II to determine their differences and similarities. We also tested different frequencies and amplitudes of stimulation to determine roles of these parameters. Submerged transverse slices of the mouse spinal cord were used to test responses of neurons and glial cells of lamina II. Blind whole-cell recordings were made before, during and after exposure of a slice to kHz-frequency stimulation. kHz-FS frequencies ranged from 2 to 10 kHz and amplitudes ranged from 2 to 10 mA. Temperature of the ACSF was monitored with an optical thermistor (dimensions 100x100x100μm) placed on a slice near a recorded cell. During kHz-FS the temperature at a recorded point invariably increased. ΔTºC was within +0º to +3ºC window depending on Frequency/Amplitude composition. All neurons responded with various degrees of depolarization, changes in Rin, Rh and spike threshold. None of the changes by its own correlated with a temperature change. However, both ΔTºC and ΔVm showed direct correlation with kHz-FS amplitude and inverse correlation with kHz-FS frequency, indicating dependence of the effect on the overall energy released by passing current. Stimulation with High Frequency/High Amplitude or Low frequency/Moderate Amplitude was often lethal to neurons. Responses of glial cells were similarly depolarizing with Rin changing differently in different glial cells. Many glial cells demonstrated a transient sustainability to incremental increase of stimulation intensity. But this “buffering” could be abruptly broken at some unpredictable moment resulting in a sudden strong depolarization. If kHz-FS in such cases was cancelled before complete loss of Vm, this “break” could be reversed, returning Vm to a pre-FS level. Response thresholds in glial cells were on average higher than in neurons, but their ranges overlapped. Response of neurons and glia should influence each other during kHz-FS. Therefore, glial response undoubtedly has an impact in the overall response to kHz-FS in the dorsal horn. It must be considered while studying mechanisms of kHz-FS anesthetic action in experimental and clinical practice.

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Poster

PSTR009: Intrinsic Properties: Diversity and Function

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.22/B93

Topic: A.03. Stem Cells and Reprogramming

Title: Electrophysiological profiling the functional properties of human NGN2 neurons

Authors: *R. E. PETROSKI[1], C. M. PETROSKI[1], D. LIU[1], S. GRIGORYEV[1], M. HE[1], K. LEE[2], C. A. HINCKLEY[2];
[1]Neuroservices-Alliance, San Diego, CA; [2]Biogen, Cambridge, MA

Abstract: Human iPSC-derived neurons promise to be a relevant in vitro model of human neuronal function and are hypothesized to predict the efficacy of novel therapeutics for neuroscience indications. The phenotypes of hiPSC-derived neurons have been primarily characterized by mRNA expression. Very few reports describe the functional properties by electrophysiological methods. We describe the functional properties of an NGN2-derived cell line by both patch clamp and microelectrode array recording (HD-MEA). NGN2 neurons were plated at low density on a confluent monolayer of rat astrocytes. The acquisition of a mature electrophysiological phenotype was monitored with time culture. The neurons exhibited a negative resting membrane potential very early. Not surprisingly, the neurons grew larger with time in culture as measured by increased whole cell capacitance and decreased input resistance. The percentage of neurons exhibiting spontaneous action potential firing also increased with time in culture. Spontaneous postsynaptic currents were also detected indicating that the NGN2 neurons formed functional synapses. We detected NMDA receptor currents in ~50% of the NGN2 neurons. We also profiled the activity of NGN2 neurons using the MaxTwo HD-MEA (MaxWell Biosciences) that simultaneously records up to 1,020 neurons from 6 independent wells. In agreement with the patch clamp results, spontaneous activity increased with time in culture. The mean firing rate was ~1 Hz. NGN2 neurons in culture exhibited network connectivity as seen by coherent bursting with a frequency of ~0.2 Hz and a burst duration of ~0.8 sec. Co-culturing the excitatory NGN2 neurons with human iCellGABA inhibitory neurons (Fujifilm) decreased the spontaneous activity of NGN2 neurons.

Disclosures: R.E. Petroski: A. Employment/Salary (full or part-time):; Neuroservices-Alliance. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Biogen. **C.M. Petroski:** A. Employment/Salary (full or part-time):; Neuroservices-Alliance. **D. Liu:** A. Employment/Salary (full or part-time):; Neuroservices-Alliance. **S. Grigoryev:** A. Employment/Salary (full or part-time):; Neuroservices-Alliance. **M. He:** A. Employment/Salary (full or part-time):; Neuroservices-Alliance. **K. Lee:** A. Employment/Salary (full or part-time):; Biogen. **C.A. Hinckley:** A. Employment/Salary (full or part-time):; Biogen.

Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.01/B94

Topic: B.07. Network Interactions

Support: AGM and EH thank the Krembil Foundation for their generous funding support
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Title: Dose prediction of α5-GABA receptor modulation from simulated EEG of depression severity

Authors: *A. GUET-MCCREIGHT[1], F. MAZZA[2], T. D. PREVOT[3], E. SIBILLE[4], E. HAY[1]; [1]Krembil Ctr. for Neuroinformatics, Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada; [2]Dept. of Physiol., Krembil Ctr. for Neuroinformatics, Toronto, ON, Canada; [3]Ctr. For Addiction and Mental Hlth., Toronto, ON, Canada; [4]CAMH - Univ. of Toronto, Toronto, ON, Canada

Abstract: Treatment for major depressive disorder (depression) often has partial efficacy and a large portion of patients are treatment resistant. Recent studies implicate reduced somatostatin (SST) interneuron inhibition in depression, and new pharmacology boosting this inhibition via positive allosteric modulators of α5-$GABA_A$ receptors (α5-PAM) offers a promising effective treatment. However, testing the effect of α5-PAM on human brain activity is limited, meriting the use of detailed simulations. We utilized our previous detailed computational models of human depression microcircuits with reduced SST interneuron inhibition and α5-PAM effects, to simulate EEG of virtual subjects across depression severity and α5-PAM doses. We developed machine learning models that predicted optimal dose from EEG with high accuracy and recovered microcircuit activity and EEG. This study provides dose prediction models for α5-PAM administration based on EEG biomarkers of depression severity. Given limitations in doing the above in the living human brain, the results and tools we developed will facilitate translation of α5-PAM treatment to clinical use.

Disclosures: A. Guet-Mccreight: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); All Authors: Patent. Title: EEG Biomarkers for alpha5 PAM dosage determination and therapeutic monitoring, 63/382,577, ES and TP: Patent. Title: Treatment of Cognitive and mood systems in Neurodegenerative and Neuropsychiatric disorders with Alpha 5 – containing GABAA selective agonist, 62/310409, ES and TP: Patent. Title: Compositions And Methods Relating To Use Of Agonists Of Alpha5-Containing Gabaa Receptors, 62/805009, ES and TP: Patent. Title: Imidazobenzodiazepines for treatment of cognitive and mood symptoms, PCT/US2022/042832, ES is Founder of Damona Pharmaceuticals, a biopharma dedicated to bringing α5-PAM compounds to the clinic., TP is Director of Operations of Damona Pharmaceuticals, a biopharma dedicated to bringing α5-PAM compounds to the clinic.. **F. Mazza:** None. **T.D. Prevot:** None. **E. Sibille:** None. **E. Hay:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.02/B95

Topic: B.07. Network Interactions

Support: JSPS KAKENHI JP23H05476

Title: A microcircuit model for chunking reward-driven replay in the hippocampus

Authors: *H. MUSSET[1], T. FUKAI[2];
[1]Okinawa Inst. of Sci. and Technol., Onna-son, Okinawa-ken, Japan; [2]Okinawa Inst. of Sci. and Technol., Onna-son, Japan

Abstract: Increasing amounts of experimental and theoretical evidence place hippocampal replay as a substrate for memory consolidation and retrieval in mammals. Nested in sharp-wave ripples (SWR), short high-frequency oscillatory bouts occurring during slow-wave sleep and awake immobility, replay describes trajectories through space by sequentially reactivating place cells. Crucially, reward and behaviorally salient locations are overrepresented in replay specifically at termination, which is assumed to be an important property of goal-directed learning. While there is evidence hinting at the role of inhibition buildup in sharp-wave ripple termination, previous theoretical modeling work fails to provide explanatory evidence linking reward overrepresentation and replay termination. Here we propose a biologically plausible circuit-level model of CA3 pyramidal cells and interneurons in which reward is overrepresented at termination. In our model, associations between pyramidal place cells are learned through symmetric spike-timing-dependent plasticity during simulated exploration of an environment. This recurrently connected population of pyramidal cells interacts with two major hippocampal interneuron populations, parvalbumin-expressing and cholecystokinin-expressing basket cells (PVBC and CCKBC respectively) as well as with a recently discovered inhibitory neuron population active exclusively during SWRs (TORO — theta-off, ripple-on). In this model, PVBC and CCKBC populations are responsible for bistability between SWR and non-SWR states in the resting states (excluding theta-dominated states during REM sleep and locomotion) and TORO cells act as a switch through feedback from the reward-associated place cells, thus terminating replay at reward. This model is able to reproduce previously seen results of replay and can assess how replay contents are affected by previously learned associations and environments, which is notably difficult to achieve experimentally. Further, our model also predicts differences in durations of replays depending on the proximity of the decoded position to reward at termination, and preliminary analyses of replay duration in rats performing open-field and linear maze memory tasks support this prediction.

Disclosures: **H. Musset:** None. **T. Fukai:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.03/B96

Topic: B.07. Network Interactions

Support: GM056398

Title: Spiking neuronal network model with biologically plausible learning rule reproduces cortical firing patterns in wakeful and anesthetized states

Authors: *C. CHAN[1], A. G. HUDETZ[2];
[1]Biomed. Engin., Univ. of Michigan, Ann Arbor, MI; [2]Dept. of Anesthesiol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Modeling neuronal activity patterns by spiking neural networks (SNNs) is a promising approach to gain insight into the functional organization of brain circuits and how it is modified in altered functional states. To this end, biologically plausible SNN models that recap ontogenetic development are preferred but have been sparsely utilized. Here we demonstrate the feasibility of training an SNN, composed of Izhikevich neurons on real spiking data using the biologically plausible learning rule, eligibility propagation (e-prop) which does not rely on backpropagation. We aimed to mimic the firing pattern of neurons recorded in the visual cortex of rats in vivo during wakefulness and under three levels of anesthesia as produced by the anesthetic desflurane at 6%, 4%, and 2% inhaled concentrations (Lee et al, 2020). Spiking neural data were continuously fed into the SNN to achieve continuous learning. The SNN has a network size of 65 neurons and the initial weights were set to sparse and randomly connected configuration, resembling those of an immature brain. Dale's rule was applied to the SNN and connectivity was fixed during weight update. The cost function was designed to reduce the difference between the firing rates of the SNN and of the recorded data. We evaluated the synchrony between the SNN's firing rate patterns and the recorded data by using dynamic correlation and decoding accuracy. In 3 rats we were able to decode the dose levels from the firing patterns of the trained SNNs with 90.6% (SD 15.9%) accuracy and 0.78 (SD 0.10) dynamic correlation. With connectivity constraint omitted during the weight update, the decoding accuracy and dynamic correlation dropped to 57.0% (SD 13.1%) and 0.10 (SD 0.08) respectively. We also examined how the SNN's characteristic may influence the above two metrics. We found that 10% connectivity was optimal, and the synchronicity decreased as the connectivity varied from 10% to 90%. The decoding accuracy dropped to 68.8% (SD 15.2%) when the percentage of excitatory neurons was increased from 80% to 100%. When varying the network size from 4 to 40, the decoding accuracy increased and plateaued at 30, scaling similarly to the result obtained by decoding from the recorded data directly. Throughout the training, the SNN's weight matrix evolved from a random graph to one with higher clustering coefficient and lower average path length, thus exhibiting small-world property similar to that of a mature human brain. In conclusion, we showed that SNN can learn in a biologically plausible way to mimic state-dependent neuron firing patterns in the cortex. The implemented learning rules should help develop more complex SNN models of the brain in the future.

Disclosures: **C. Chan:** None. **A.G. Hudetz:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

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Topic: B.07. Network Interactions

Support: The Academy of Finland (decision Nos. 326494, 326495, 345280, and 355256)
European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement 945539 (Human Brain Project SGA3)

Title: Discovering Neuron-Glia Interactions: From Molecular Mechanisms to Computational Models

Authors: *T. MANNINEN, L. KETO, J. ACIMOVIC, M.-L. LINNE;
Fac. of Med. and Hlth. Technol., Tampere Univ., Tampere, Finland

Abstract: Exploring the intricate relationships between neurons and glial cells, particularly astrocytes, is critical for understanding the diverse functions astrocytes perform in maintaining brain homeostasis, integrating and modulating sensory information, and influencing cognitive processes. Understanding the interactions between neurons and glial cells is also important so that we can interpret correctly non-invasive signals measured from humans. In recent years computational models have emerged as valuable tools for dissecting neuron-glia interactions, addressing existing controversies, and advancing our comprehension of neural circuit dynamics underlying sensory information modulation. Our computational efforts synthesize decades of experimental *in vitro* and *in vivo* research studying molecular- and cellular-level neuron-astrocyte interactions in different brain areas and functions. We propose a comprehensive framework for modeling these interactions and integrate experimental findings with computational neuro- and glioscience tools. We here demonstrate the utility of our developed set of tools (Keto and Manninen, 2023) for simplifying the construction of morphologically detailed astrocyte models. Through our systematic analysis of cellular- and synapse-level models (Manninen et al., 2017, 2018, 2020; Seppälä et al., 2022) and their extension to network-level models (Linne et al., 2022; Manninen et al., 2023), we enhance the biological relevance of the models. Our examination of existing neuron-astrocyte network models (Manninen et al., 2023) explains the construction of these models and adoption of network- or population-level properties including cell distribution and connectivity, and inclusion of biophysically and biochemically relevant calcium and other ion sources. Additionally, we provide an extensive survey and recommendations of simulation tools for constructing and manipulating 3D cell morphologies and simulating models at various levels, from single-cell astrocyte models to neuron-astrocyte network models (Keto and Manninen, 2023; Linne et al., 2022). Our analyses underscore the urgent need for comprehensive experimental investigations, particularly in awake animals, to refine the computational models. By incorporating molecular-level mechanisms by which astroglia influence neurons, we can enhance our comprehension of the roles diverse neural circuits play in various brain and cognitive functions. Acknowledgements: JA is currently AstraZeneca employee, but here presented research was conducted during her previous employment at Tampere University and is unrelated to her current employment.

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Poster

PSTR010: Computational Modeling of Synaptic Networks

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Title: Modeling brain state transitions: impact of cholinergic heterogeneity in whole-brain dynamics

Authors: L. DALLA PORTA[1], A. DESTEXHE[2], *M. V. SANCHEZ-VIVES[1,3];
[1]IDIBAPS (Institut D'Investigacions Biomediques August Pi i Sunyer), Barcelona, Spain; [2]NeuroPSI, CNRS, Saclay, France; [3]ICREA, Barcelona, Spain

Abstract: The wake-sleep cycle comprises fundamentally distinct brain states, including slow wave sleep (SWS) and wakefulness. During SWS sleep, the cerebral cortex exhibits large low-frequency fluctuations that propagate as traveling waves. Conversely, during wakefulness, low-frequency activity is suppressed, and the dynamics are characterized by asynchronous irregular patterns. Although the wake-sleep cycle is known to be dependent on neurotransmitters like acetylcholine (ACh), the mechanisms by which local neuronal interactions generate large-scale brain activity patterns are not well understood (Dear et al. Nat. Neuro., 2024). Inspired by biophysically detailed mesoscale models of the cortex with spiking neurons incorporating specific neural mechanisms like M-current and adaptation currents (Dalla Porta et al., Plos Comp. Bio., 2023), we developed a whole-brain model. This model is constrained by human tractography and cholinergic gene expression (Hawrylycz et al. *Nature,* 2012). Each node was modeled using the mean-field model of Adaptive Exponential neurons, with cortical regions incorporating intrinsic properties of both excitatory and inhibitory neurons (Goldman et al. *Front. Comput. Neurosci*., 2023). Spatial variations in cholinergic expression, in the form of M1 and M2 muscarinic receptors, were introduced by adjusting local node biophysical and functional properties, thus creating a detailed virtual brain landscape. Our model successfully replicated spontaneous patterns of slow oscillations and their wave propagation properties, as well as awake-like dynamics. Heterogeneity impacted cortical properties, modulating excitability, degree of synchrony, and relations among functional and structural connectivity. Additionally, we quantified global brain complexity following stimulation using the perturbational complexity index (Gaglioti et al. Applied Sciences, 2024) to differentiate brain states and assess the impact of cholinergic heterogeneity on evoked activity. We observed a significant increase in complexity during the asynchronous state in the heterogeneous model, suggesting a closer approximation to real brain dynamics. This increased complexity reflected the spatiotemporal diversity of patterns and the intricate causal interactions across different cortical areas. Overall, our findings underscore the impact of cholinergic heterogeneity on global

brain dynamics and transitions across brain states. Our approach also offers a pathway to studying various neuromodulators involved in brain state regulation.

Disclosures: L. Dalla Porta: None. **A. Destexhe:** None. **M.V. Sanchez-Vives:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: B.07. Network Interactions

Support: NIH Grant R01MH126518

Title: Cellular mechanisms of default mode network function and dysfunction

Authors: *T.-A. E. NGHIEM[1], V. MENON[2];
[1]Stanford Univ., Palo Alto, CA; [2]Psychiatry & Behavioral Sci., Stanford Univ., Stanford, CA

Abstract: The default mode network (DMN) constitutes an ensemble of brain regions crucially involved in cognitive function and dysfunction. DMN regions emerge as a strongly coupled network during resting state and are suppressed by salient events, as well as by stimulation of the anterior insula (AI) as recently shown with optogenetic manipulation in rodents. However, the cellular-scale mechanisms that sculpt the landscape of interactions between neuronal assemblies to allow the emergence and suppression of the DMN remain fundamentally unknown. In this work, we strive to bridge the gap across spatial scales and gain a unified understanding of cellular-scale mechanisms orchestrating DMN dynamics. To this purpose, we leverage novel, biophysically informed mean-field models of neural dynamics connected along a tracer-derived whole-brain mouse connectome using The Virtual Brain simulator. Model parameters are inferred to account for functional connectivity in awake mouse fMRI. Our model can account for DMN emergence as well as suppression by AI activation as empirically observed. Further, we elucidate the specific subregional circuits that causally give rise to each DMN region's suppression. Finally, we demonstrate that imbalance between excitatory and inhibitory synaptic conductances, a cellular mechanism hypothesized to underlie symptoms across psychiatric disorders including autism spectrum disorder, can attenuate DMN suppression as seen in patients. In sum, our findings causally link cellular-scale mechanisms and subregional circuitry to large-scale dynamics of brain networks underlying cognition, with potential implications toward identification and treatment of excitation-inhibition imbalance in psychiatric conditions.

Disclosures: T.E. Nghiem: None. **V. Menon:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

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Program #/Poster #: PSTR010.07/B100

Topic: B.07. Network Interactions

Support: R35NS097185 to C.J.W

Title: Local Connections in the Globus Pallidus Enhance Entrainment to High-Frequency Inputs

Authors: *E. OLIVARES[1], C. J. WILSON[2];
[1]UTSA-College of Sci., San Antonio, TX; [2]Univ. Texas San Antonio, San Antonio, TX

Abstract: The globus pallidus externa (GPe) is populated by inhibitory neurons that fire rapidly and continuously. Due to its sparse local connectivity, each GPe neuron receives a constant high frequency barrage of IPSCs from only a few (~10) other GPe neurons. These synaptic currents are large but brief, resulting in a staccato series of inhibitory events rather than continuous inhibition. The immediate consequence of this local activity is the disruption of neurons' oscillation periodicity. Its impact on the input-output responses of GPe neurons and, consequently, the flow of information through the basal ganglia remains unclear. This work studies the effect of GPe local connections on entrainment to oscillatory inputs using a mathematical model of the GPe neuron model derived from perforated patch slice recordings and validated by predicting isolated neurons' responses to applied sinewave currents. Sinewave stimuli produce either rate modulation (at very low stimulus frequencies) or stochastic spike entrainment, in which action potentials preferentially occur within a narrow range of stimulus phases. In the absence of the barrage input, GPe neurons readily entrain at frequencies near their intrinsic firing rate, but entrainment decreases at higher rates. The barrage stimulus enhances the entrainment of GPe neurons to sinewave stimuli at all frequencies, except for frequencies near a cell’s intrinsic rate and its harmonics, at which the barrage disrupts phase locking. The underlying mechanism is revealed by the phase-time trajectories of the model neurons. An oscillating neuron becomes increasingly sensitive to synaptic inhibition at later times in its interspike interval (ISI). This is due to two factors: the shape of GPe cells' phase resetting curves, which often peak in the last quarter of their ISI, and the increasing synaptic driving force for inhibition as the cell depolarizes throughout its ISI voltage trajectory. Consequently, inhibitory synaptic current causes cells to linger at late phases. During this period, the neurons are close to firing and can be entrained to external inputs that would otherwise be too small to trigger action potentials. When connected, the neurons' entrainment profile decreases at low frequencies because the inhibitory barrage produces a current antiphase with the stimulus wave. Entrainment increases at high frequencies (above 50 Hz), because the synaptic delay causes the feedback to become additive with the applied stimulus. The net result is an increase in the effectiveness network entrainment by high frequency components of the signals arriving in the GPe from other structures, such as the striatum or subthalamic nucleus.

Disclosures: E. Olivares: None. **C.J. Wilson:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.08/B101

Topic: B.07. Network Interactions

Support: NIH MH135565

Title: Cholinergic modulation of inhibitory subnetworks and their role in information processing

Authors: *B. E. FRY[1], M. R. ZOCHOWSKI[2];
[1]Physics, Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [2]Dept. of Physics and Biophysics Program, Univ. of Michigan, Ann Arbor, MI

Abstract: Neuromodulatory differences between brain states, such as REM and NREM sleep, promote changes in both cellular and network-wide dynamics, thus controlling information storage and transmission throughout the brain. Acetylcholine (ACh) is a key modulator of neural excitability and is markedly different between the aforementioned sleep states. Further, the network structure itself is critical to determining the neural dynamics; an important feature of hippocampal and cortical networks is subpopulations of distinct inhibitory interneuron types. Hence, we explore ACh modulated changes in functional connectivity and neural activation in biophysical in-silico network models. Cholinergic modulation through M1 receptor activation is represented by slow, hyperpolarizing m-currents in conductance-based models of pyramidal cells and somatostatin-positive (SST+) interneurons, while a different subpopulation of fast-spiking parvalbumin-positive (PV+) interneurons constrains dynamics on a shorter time scale. We show that the higher excitability of SST+ interneurons during brain states with high ACh concentrations leads to competitive activation of pyramidal cells and corresponding PV+ interneurons, while disinhibition during low ACh states promotes broad, synchronized activity that mediates memory engram consolidation. Additionally, the different spatial extents of fast-spiking and SST+ interneuron connectivity, in combination with differing synaptic time scales, allow the network structure to alter the precise spatiotemporal effects of cholinergic modulation. Altogether these results pinpoint the importance of cholinergic modulation of inhibitory subnetworks and their differential roles in information processing.

Disclosures: B.E. Fry: None. **M.R. Zochowski:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.09/B102

Topic: B.07. Network Interactions

Support: Ontario Graduate Scholarship

Title: Impaired dendritic signal integration in human cortical microcircuit models in depression

Authors: *H. YAO[1], E. HAY[2];
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada

Abstract: Major depressive disorder (depression) is associated with altered dendritic mechanisms in excitatory cortical pyramidal (Pyr) neurons, due to decreased inhibition from somatostatin (SST) interneurons and a loss of spines and their associated synapses, as indicated in postmortem human data. Dendrites play an important role in signal processing as they receive the majority of synaptic inputs and exhibit nonlinear properties such as backpropagating action potentials and dendritic Na+ spikes that enhance the neuron's computational power. However, it is currently unclear how dendritic changes in depression impact the integration of signals. Here, we expanded our previous data-driven models of human cortical microcircuits in health and depression to include active dendritic properties that enable backpropagating action potentials as measured in human neurons, and spine loss in depression in terms of synapses loss and altered intrinsic property. We show that the altered intrinsic properties due to spine loss abnormally increase the amplitude of backpropagating action potential and abolish nonlinear dendritic integration of signals at the single neuron and microcircuit levels. Our study thus mechanistically links cellular changes in depression to impaired dendritic processing in human cortical microcircuits.

Disclosures: H. Yao: None. **E. Hay:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

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Program #/Poster #: PSTR010.10/B103

Topic: B.07. Network Interactions

Support: NIH MH135565

Title: Cholinergic regulation of network dynamics mediates switching between memory activation and reactivation modes during different vigilance states.

Authors: *Z. NOUREDDINE[1], M. R. ZOCHOWSKI[1,2];
[1]Dept. of Physics, [2]Biophysics Program, Univ. of Michigan, Ann Arbor, MI

Abstract: Neuromodulatory mechanisms in the brain control network dynamics, and can critically switch its function. Here, we investigate the role of changing cholinergic levels during different vigilance states in modulating information processing during spatial tasks. ACh is a potent neuromodulator that is typically high during active waking and low during quiet waking and influences network dynamics via various synaptic and cellular mechanisms. We model the different vigilance states by modeling the effects of Acetylcholine concentrations through the M1

receptor pathway. Specifically, we simulate a complex maze run during which a rat traverses a maze composed of multiple junctions, represented spatially by the activation of a network of excitatory neurons. We show that variations in ACh levels change the network-wide E/I balance driving distinct activation patterns in the network. Specifically, high ACh concentrations, associated with active waking, activate only local neuronal representations that code for spatially limited features of the memory. In contrast, low ACh concentrations, associated with quiet waking, synchronously reactivate long-range paths representing an extended memory trace. This differential activation and subsequent consolidation of different memory features via spike timing dependent plasticity (STDP) allows for more efficient consolidation of the experienced trajectory. In all, our results indicate that ACh may play a key role in controlling the interplay between online memory storage and offline memory consolidation during various vigilance states.

Disclosures: Z. Noureddine: None. **M.R. Zochowski:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

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Topic: B.07. Network Interactions

Support: JP21H05137
JP

Title: Propagation of gamma oscillations through topographic connections in a connectome-based spiking neural network model of the mouse sensorimotor cortex

Authors: *J. IGARASHI[1], Z. SUN[2], T. YAMAZAKI[3], Y. ISOMURA[4], R. HIRA[5];
[1]Ctr. for Computat. Sci., RIKEN, Wako, Saitama, Japan; [2]Juntendo Univ., Inzai-shi, Japan; [3]The Univ. of Electro-Communications, Chofu-shi, Japan; [4]Physiol. and Cell Biology, Grad. Sch. of Med. and Dent. Sci., [5]Tokyo Med. and Dent. Univ., Bunkyo-ku, Japan

Abstract: Sensorimotor cortical regions interact through topographic connections to process movement behaviors and somatosensory information. However, it remains unclear what spatiotemporal neural activity occurs for their coordination through the connections. To investigate this, we developed a spiking neural network model of the mouse sensorimotor cortex based on the information on the electrophysiological data and the mouse brain atlas with connectome provided by Allen Institute [1]. The model consisted of the primary and secondary motor cortex (M1 and M2) and the primary and secondary somatosensory cortex (S1 and S2) in the left hemisphere. Positions of model neurons were generated using the neural density and the brain atlas in 100-micron voxel resolution. We generated intra-regional connections among the neurons in the same regions based on the local circuit information, such as patch-clamp recordings and laser scanning photo-stimulation, as in the previous study [2]. We generated

inter-regional connections among neurons in the different regions using the connection strength of voxel-to-voxel connectome as connection probability [1]. We used the leaky integrate-and-fire neuron and conductance-based synapse models for all neurons and synapses. We used an in-house spiking neural network simulator, the MONET, which runs on CPU-based distributed computers. To investigate spatiotemporal interactions among sensorimotor regions, we stimulated three locations corresponding to different body parts in the M1, located at rostral, intermediate, and caudal parts. The 100 ms step current was given to excitatory and inhibitory cells in one voxel of layer 2/3 in the M1. With the M1 stimulation, neurons in the M2 neighboring the M1 stimulation site mainly exhibited their activation. This result means that the M1 activated the M2 that represented the same body parts through the topographic connections contained in connectome. Interestingly, the activated neurons in both M1 and M2 were synchronized in the gamma frequency range (30-50 Hz), which means that the gamma oscillation propagated from M1 to the neighboring M2 through the topographic connections. When we stimulated neurons in layer 3 of S1, neurons in the M1 that neighbored the stimulated S1 were synchronized in the gamma frequency range. These results suggest that distributed sensorimotor information may be coordinated with oscillatory neural activity through the topographic connections across the sensorimotor regions. [1] Knox, et al., (2019) Network Neuroscience, 3, 217. [2] Igarashi, et al., (2019) Frontiers in Neuroinformatics, 13, 1-15.

Disclosures: **J. Igarashi:** None. **Z. Sun:** None. **T. Yamazaki:** None. **Y. Isomura:** None. **R. Hira:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

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Topic: B.07. Network Interactions

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Title: Biomemetic multiscale simulation of corticostriatal circuit for exploring receptor level mechanisms underlying pharmacological intervention.

Authors: *A. PATHAK[1], E. K. MILLER[2], L. R. MUJICA-PARODI[3], H. STREY[4], R. H. GRANGER, Jr.[1];
[1]Dartmouth Col., Hanover, NH; [2]The Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [3]Dept. of Biomed. Engin., Athinoula A. Martinos Ctr. for Biomed. Imaging, Stony Brook, NY; [4]Stony Brook Univ., Stony Brook, NY

Abstract: In the presence of a given centrally-active chemical compound, what receptors are activated at what brain locations, how may those affect various oscillatory activity patterns, and how might these in turn cascade to modify overall behavior of the system? We leverage our unique multiscale biomimetic modeling approach to study these questions, to aid in the understanding of drug effects in the brain. We begin with observed effects of propofol and ketamine in macaque and human subjects, along with a range of documented physiological and behavioral measures. We recently have constructed an extensive corticostriatal computational model that incorporates phenomena from receptor-specific activity, to cell spiking, to local field potentials, to large-scale field activity across multiple brain areas [1]. We have shown the ability of that model to i) explain complex behavioral and dynamical physiological phenomena in nonhuman primates (NHPs) using anatomically-determined synaptic level mechanisms and modulatory influences; ii) generating substantial, unexpected, and subsequently verified predictions about specific physiological responses and their computational implications. Thus we view the modeling approach as well suited to explore the interplay among receptors, transmitters, and modulators, that affect behavioral and mental states such as arousal and attention, and their relationship with field measures such as alpha or beta oscillations. Compounds such as propofol and ketamine have receptor-level effects that challenge the balance among various circuit elements such as excitation/inhibition and their distinct time course. The resulting findings may help illuminate mechanisms that underlie brain-circuit phenomena in healthy as well as disordered brains. References: [1] A Pathak, et al., New learning principles emerge from biomimetic computational primitives. bioRxiv: The Prepr. Serv. for Biol. (2023).

Disclosures: **A. Pathak:** None. **E.K. Miller:** None. **L.R. Mujica-Parodi:** None. **H. Strey:** None. **R.H. Granger:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

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Program #/Poster #: PSTR010.13/B106

Topic: B.07. Network Interactions

Support: Grant GR43782

Title: Spike synchrony in mitral and tufted cell subnetworks in OB subcircuit model

Authors: *E. A. SMITH[1], J. BIRGIOLAS[1], S. M. CROOK[2];
[1]Sch. of Life Sci., Arizona State Univ., Tempe, AZ; [2]Sch. of Mathematical and Statistical Sci., Arizona State Univ., Tempe, AZ

Abstract: Oscillations in local field potentials arise from synchronized activity of many neurons, but the contributions from individual cells are not apparent from this aggregate signal. In the rodent olfactory bulb (OB), the excitatory projection neurons - mitral and tufted cells (M/TCs) - have different physiological properties and connectivity patterns, causing distinct subnetworks

within the OB that independently contribute to network activity. It is still not fully clear how the MC and TC subnetworks each modulate OB oscillations in different frequency ranges, specifically beta (15-40 Hz), gamma (30-80 Hz), and high frequency (130-180 Hz) oscillations. In response to odors, nearly all TCs show spike synchrony in gamma ranges of ~40-100 Hz, while only about half of MCs show spike synchrony, concentrated between ~40-60 Hz. Beta and gamma oscillations alternate, with odor-induced gamma oscillations occurring at the inhale-exhale transition, and beta at the end of exhalation. We use a biophysically realistic mouse OB subcircuit model to better understand how dendrodendritic interactions between granule cells (GCs) and M/TCs impact spike synchrony in oscillations across beta, gamma, and high frequency ranges. This model contains a M/T/GC network with realistic 3D morphologies, connectivity, and simulated odor inputs, and provides a platform for in silico physiology experiments. Odor inputs are simulated using a realistic representation of experimentally-recorded spatial activity patterns elicited in the glomerular layer by natural odors, modeled as spike inputs to the M/TC apical dendrites. With simulated odor inputs, gamma oscillations are slightly out of phase from beta oscillations across simulated sniffs, but do not show clear switching between the oscillatory regimes. Spike-time synchrony in TC models was robust across gamma frequencies, while MC model synchrony was concentrated in lower range gamma frequencies. A greater proportion of TC models show gamma synchrony than MCs, and TC models show stronger HFO-band spike-time synchrony than MCs. Sister MCs or TCs, which have apical dendrites that converge within the same glomerulus in the network model, show greater spike-time synchrony.

Disclosures: **E.A. Smith:** None. **J. Birgiolas:** None. **S.M. Crook:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.14/B107

Topic: B.07. Network Interactions

Support: NIH grant R01MH112746
NIH grant R01MH108590
SFARI Pilot Award

Title: Personalized circuit modeling captures variation in cortical functional connectivity

Authors: *R. COOPER[1], M. DEMIRTAS[2], J. B. BURT[1], A. M. HOWELL[3], J. JI[4], G. REPOVŠ[5], S. N. SOTIROPOULOS[6], A. ANTICEVIC[2], J. D. MURRAY[7];
[1]Physics, Yale Univ., New Haven, CT; [2]Psychiatry, Yale Univ., New Haven, CT; [3]Neurosci., Yale Univ., New Haven, CT; [4]Yale Univ., New Haven, CT; [5]Univ. of Ljubljana, Ljubljana, Slovenia; [6]Univ. Oxford, Oxford, United Kingdom; [7]Dept. of Psychiatry, Yale Univ., New Haven, CT

Abstract: Functional magnetic resonance imaging (fMRI) of the human cortex reveals patterns of correlated neural dynamics that are individual-specific and associated with phenotypic variation. However, circuit mechanisms underlying individual variation in functional connectivity (FC) are not well understood. Here, we fit individual-level FC patterns with a biophysically-based circuit model of large-scale cortical dynamics. This model is fit with a small number of neurophysiologically interpretable parameters and incorporates a hierarchical gradient in local synaptic strengths across cortex parameterized via the structural MRI-derived T1w/T2w map. We applied our modeling framework to resting-state fMRI FC from a large cohort of subjects (N=842) from the Human Connectome Project. We found that the model captures a substantial portion of individual variation in FC, especially with personalized degrees of local synaptic specialization along the hierarchical gradient. Empirically, we found that principal modes of individual variation in FC follow interpretable topographic patterns. We developed a framework to assess model expressivity via how these empirical modes of FC variation align with variations in simulated FC induced by parameter perturbations. This framework reveals a straightforward mapping between key parameters and the leading modes of variation across subjects and provides a principled approach to extending computational models. Collectively, our modeling results establish a foundation for personalized computational modeling of functional dynamics in large-scale brain circuits.

Disclosures: R. Cooper: None. **M. Demirtas:** None. **J.B. Burt:** None. **A.M. Howell:** None. **J. Ji:** None. **G. Repovš:** None. **S.N. Sotiropoulos:** None. **A. Anticevic:** None. **J.D. Murray:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.15/B108

Topic: B.07. Network Interactions

Title: Exploring the Influence of SOM and PV on Neuronal Criticality and Information Processing in Schizophrenia: Balancing Excitatory and Inhibitory Cell Dynamics

Authors: *J. (. JUNG[1], D. W. DOHERTY[2], A. NEWTON[3], S. DURA-BERNAL[3], A. BALLA[4], M. N. O'CONNELL[4], D. C. JAVITT[5], W. W. LYTTON[6], S. A. NEYMOTIN[4];
[1]SUNY downstate health science university, Brooklyn, NY; [2]Dept. of Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Pittsburgh, PA; [3]Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [5]Ctr. for Schizophrenia Res., [4]Nathan Kline Inst., Orangeburg, NY; [6]Physiology/Pharmacology, DHSU, Brooklyn, NY

Abstract: Postmortem studies have shown reductions in somatostatin (SOM) (30-51%) and parvalbumin (PV) (17-31%) positive interneurons in patients with schizophrenia (SZ). These reductions are linked to cognitive impairments, including learning and memory deficits, and sensory system dysfunction. Our study explores the roles of SOM and PV interneurons in

modulating neuronal criticality within a biophysically detailed, multi-layer mouse motor cortex (M1) model. We investigate how these interneurons influence the network's critical state and regulate neuronal avalanches and bursts.Preliminary results suggest that SOM interneurons prolong intervals between avalanches, affecting timing and rhythm. Conversely, PV neurons shorten intervals, indicating a specialized role in synaptic response and network reactivation. Our simulations reveal prolonged NMDA receptor-mediated currents in intratelencephalic (IT) cells during silent periods between avalanches, priming them for bursts. This is relevant to SZ, where NMDAR hypofunction is well-documented. NMDAR dysfunction in interneurons may disrupt the balance between excitatory and inhibitory signals needed for normal brain function. Our findings highlight a potential pathway contributing to disrupted network behaviors in SZ.Using the NEURON/NetPyNE framework and a detailed mouse motor cortex model, we manipulate inhibitory neurons to assess their impact on network dynamics. We focus on modulating NMDAR and GABAB expression in SOM cells, which express both GABAA and GABAB receptors, while PV cells express only GABAA. We analyze SOM cell projections to dendrites and synaptic NMDA currents in IT cells to determine how these changes influence neuronal avalanches. Our analysis includes power-law distributions of avalanche sizes and durations to explore shifts in network criticality.Initial results show that adjusting NMDA currents impact burst initiation, with decreased SOM levels shortening the silent intervals before avalanches. Further research will explore strategic modulation of dendritic currents to regulate these intervals and potentially restore normal brain function in SZ. Insights from this study may lead to new strategies targeting GABAB and NMDA currents to correct network dysfunctions in SZ and other disorders.

Disclosures: J.(. Jung: None. **D.W. Doherty:** None. **A. Newton:** None. **S. Dura-Bernal:** None. **A. Balla:** None. **M.N. O'Connell:** None. **D.C. Javitt:** None. **W.W. Lytton:** None. **S.A. Neymotin:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.16/B109

Topic: B.07. Network Interactions

Support: NIH Grant R01NS109553
NIH Grant RF1NS132913

Title: Local vs. global slow waves in a large-scale thalamocortical network model of the human brain

Authors: *G. NAVAS[1], B. MARSH[4], B. ROSEN[5], Y. SOKOLOV[6], E. DELANOIS[2], O. C. GONZALEZ[7], G. P. KRISHNAN[8], E. HALGREN[9], M. V. BAZHENOV[3];
[1]UCSD, SAN DIEGO, CA; [2]UCSD, San DiegoSan Diego, CA; [3]Dept. of Med., UCSD, La Jolla, CA; [4]UCSD Dept. of Neurosciences, La Jolla, CA; [5]Washington Univ. in St. Louis, Saint Louis,

MO; [6]Med., UC San Diego, La Mesa, CA; [7]Dept. of Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA; [8]Georgia Inst. of Technology, Atlanta, SOCORRO, NM; [9]Multimodal Imaging Lab. (MC0841), Univ. of California at San Diego, San Diego, CA

Abstract: Slow-wave sleep (SWS) is a major brain state during non-rapid eye movement (NREM) sleep and it plays a key role for memory consolidation. It is characterized by slow oscillations (SO, < 1 Hz), alternating between active ("up") and silent ("down") states in the thalamocortical network. While traditionally viewed as a whole-brain state, recent evidence suggests that SO can be localized. Existing sleep models are generally small-scale or employ neural-mass representations, which limits investigations into how local and global SO emerge from spiking dynamics, local circuits and large-scale connectivity. To address this gap, we developed a multi-scale, whole-brain thalamocortical network model of SWS with realistic cortical connectivity. It includes 10,242 cortical columns across one hemisphere, each with six layers containing pyramidal and inhibitory neurons, and a thalamus with thalamocortical and reticular neurons. Long-range cortical connectivity and synaptic delays are based on diffusion MRI (dMRI) tractography from the Human Connectome Project (HCP).
The model predicted the existence of mixed spatio-temporal SWS states where periods of global slow-wave activity (i.e. slow waves propagating through the entire cortical hemisphere) were intermittent with periods of mostly local and non-synchronized slow waves. We found LFP-based "regularity" to adequately characterize local, mixed and global dynamics, with global dynamics yielding higher regularity. Moreover, we showed that the overall strength of synaptic excitatory connectivity is a good predictor of network dynamics, with stronger connections leading to exclusively global SO. To validate the model, we analyzed continuous stereo-electroencephalography telemetry data from 236 patients with focal epilepsy. Models with mixed states were closest to the data including (1) spatial coherence profiles from human subjects, where coherence decayed exponentially with distance and frequency, and (2) measures of functional connectivity, such as percent of connected components and number of communities. Our findings shed light on how the spatio-temporal properties of SO emerge from local and global cortical connectivity and provide a framework for further exploring the mechanisms and functions of SWS in health and disease.

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Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.17/B110

Topic: B.07. Network Interactions

Support: NIH R01NS109553
NSF GRFP DGE-2038238

Title: Differential effects of electrical stimulation across species

Authors: *B. MARSH[1], S. WILSON[2], E. HALGREN[3], M. V. BAZHENOV[4];
[1]The Univ. of California San Diego, La Jolla, CA; [2]UCSD Dept. of Neurosciences, La Jolla, CA; [3]Multimodal Imaging Lab. (MC0841), Univ. of California at San Diego, San Diego, CA; [4]Dept. of Med., UCSD, La Jolla, CA

Abstract: Cortical stimulation is emerging as an experimental tool in basic research and a promising therapy for a range of neuropsychiatric conditions. Despite its critical importance in experimental and clinical neuroscience, there is currently no systematic method to predict which neural elements will be activated by a given stimulation regime. This limitation is particularly pronounced when simulating human brain responses, as morphological data on human neurons are especially scarce.
In this project, we aimed to combine physics, biology, and computer science to simulate the effects of various levels of electrical stimulation on individual cortical neurons. Specifically, we utilized the morphology and properties of axonal arborization profiles of pyramidal cells and inhibitory interneurons from rats, mice, and humans across all cortical layers (5 layers in rodents, 6 layers in humans) obtained from publicly available anatomical reconstructions to derive the dependence of activation probability on cell type, layer, and distance from the source. This allowed us to compare response probabilities across cell types, layers, and species. These response probabilities were then incorporated into multilayer cortical network models to examine the propagation of electrical stimulation across cortical columns.
We found that cell response probability for a given stimulation strength decreased with increasing layer depth and species size, as well as generally stronger responses to anodal than to cathodal stimulation of the same strength. Additionally, rat and human neurons showed the most qualitatively similar response patterns. Rat neuron reconstructions simulated with human parameters (cortical depths, current amplitudes, etc.) further provided a reasonable estimate of the responses of human neurons. If this proves to be a generalizable trend, this may allow for much more accessible rat cells to be used to accurately predict human cell response probabilities under a variety of experimental conditions. Our approach could further be used by experimental scientists to test species-specific hypotheses in silico to select the appropriate subset of parameters for in vivo work. In summary, this project both builds new knowledge of cross-species cell response probabilities and contributes to tool building for more informed and efficient experimental protocols.

Disclosures: **B. Marsh:** None. **S. Wilson:** None. **E. Halgren:** None. **M.V. Bazhenov:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.18/B111

Topic: B.07. Network Interactions

Support: ONR N00014-22-1-2453
N00014-21-1-2290
The JPB Foundation
The Baszucki Brain Research Fund

Title: A biomimetic brain circuit simulation discovered a novel neural code

Authors: A. PATHAK[1], S. L. BRINCAT[2], E. G. ANTZOULATOS[3], E. K. MILLER[2], H. STREY[4], L. R. MUJICA-PARODI[5], *R. GRANGER[1];
[1]Dartmouth Col., Hanover, NH; [2]MIT, Cambridge, MA; [3]Univ. of California, Davis, Davis, CA; [4]Stony Brook Univ., Stony Brook, NY; [5]Dept. of Biomed. Engin., Athinoula A. Martinos Ctr. for Biomed. Imaging, Stony Brook, NY

Abstract: What are the biological building blocks of cognition? Answering this ideally requires a model that captures multiple scales from individual neurons to overall brain regions. Many models identify a balance between low-level biological detail and high-level emergent cognitive operations, attempting to address the initial question that ties biology to cognition: how can these physiologies create these computations? Any specific set of experiments are highly underspecified: their findings can be fitted by a broad range of highly different operations. There is a clear need for modeling approaches that are constrained across multiple levels, from cells to temporal activity to systems-level interactions to overt behaviors. Such an array of multiple constraints could help understand relationships across levels, such as circuit synchronies, decisions, delayed actions, generalizations, behavioral successes, and failures. We present a simulation approach in which the only tools are bottom-up physiology and anatomy, which are invoked to engage in experimental conditions, perceiving stimuli and acting appropriately in accordance. We present a fixed set of richly designed tasks that incorporate visual perception, categorization, working memory, decision-making, reward, and repeated trials. The task-set is presented both to nonhuman primates (macaques, NHPs), and to the brain simulation. Our model was uniquely successful in the following two ways: 1. Correspondence with empirical data :It generated the learning behaviors, neural spiking, field potentials, synchrony, timing, phase locking, and more, all of which showed close correspondence to those measured in the NHPs. 2. Discovery of novel phenomena: It made a remarkable discovery of an unexpected neural coding, in which certain straightforward cell spiking patterns, in response to a visual stimulus, were directly predictive of an upcoming incorrect behavioral response; the predictive code occurred hundreds of milliseconds prior to the response itself. These "incongruent" spiking patterns were found to be statistically highly predictive of correct vs. incorrect subsequent behavioral responses. The responses had never been noted in the NHP experiments, but after the simulation patterns were identified, the same predictive response was then indeed found in the empirical NHP data. Such a discovery, arising solely from simulated physiological data, is rare and is indicative of the potential power of the approach.

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Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.19/B112

Topic: B.07. Network Interactions

Title: The Effect of Noise Structure on Spatio-Temporal Pattern Formation and Chaos

Authors: *S. CHIPMAN, B. DOIRON;
Univ. of Chicago, Chicago, IL

Abstract: The goal of this work is to consider the impact of temporally and spatially correlated noise on chaotic dynamics and pattern formation in two-dimensional spatially extended recurrent networks of excitatory and inhibitory neurons. Previous work has shown that such systems exhibit spatio-temporal chaos in some regimes of their phase spaces, and fixed-point or bulk-oscillatory patterns in others. These dynamics are robust to the addition of temporally-correlated, yet spatially uncorrelated, external fluctuations (noise). Though under the correct conditions, such noise expands the chaotic regime. We find that for sufficiently high-intensity spatially-correlated noise, increasing the length of spatial correlations shrinks both the fixed-point and chaotic regions of phase space, as well as destabilizing bulk oscillations. The relative spatial scales of excitation, inhibition, and noise dictate the impact of the noise correlations on firing rate dynamics. If the spatial scale of inhibition is less than that of excitation, at high inhibitory time scales there is a region of stable bulk-oscillation followed by a weakly chaotic band. Increasing the spatial correlation of the noise takes both the stable fixed points and the weakly chaotic points to marginal points. Chaos that is robust to noise correlations primarily occurs when the spatial scales of inhibition and excitation are approximately balanced. As the spatial scale of noise increases, it severely degrades the auto-correlation of the firing rates when the system is in the fixed-point and bulk-oscillation regimes. Increasing the time scale of the noise beyond that of excitation also has the effect of suppressing both chaos and fixed-point regions. We conclude that spatial noise structure has critical implications for neuronal network dynamics and both the creation and suppression of emergent low dimensional chaotic solutions.

Disclosures: S. Chipman: None. **B. Doiron:** None.

Poster

PSTR010: Computational Modeling of Synaptic Networks

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.20/B113

Topic: B.04. Synaptic Transmission

Support: NIH NS011613
NIH 1R43NS125749
NIH 5R44MH119842

Title: Using real-time dynamic clamp to synapse living neurons with in silico neurons

Authors: *M. W. NOWAK[1], B. K. PANAMA[2,1], S. ACHARYA[1], R. V. ORTIZ[2], L. W. KORBEL[1], L. NILSSON[1], M. L. HINES[3], N. T. CARNEVALE[3], G. C. L. BETT[2,1], R. L. RASMUSSON[2,1];
[1]Cytocybernetics, Buffalo, NY; [2]SUNY at Buffalo, Buffalo, NY; [3]Yale Univ., New Haven, CT

Abstract: We explored the ability of dynamic clamp as a tool for studying synapsing transmission *in vitro* using living neurons with each other or with *in silico* neurons (termed "Cell to Cell Mode"). The modified dynamic clamp system (Cytocybernetics) calculates a synaptic current using the voltage of the "pre-synaptic" neuron. This calculated synaptic current is then input into the "post-synaptic" neuron. We combined Cell to Cell Mode with our ability to interface our dynamic clamp system with the NEURON simulator (www.neuron.yale.edu). For these preliminary studies, we synapsed human pluripotent stem cell-derived GABAergic neurons (hiPSC-GNs) (iCell-GABA Neurons, Fujifilm Cellular Dynamics) with a complex *in silico* NEURON Purkinje neuron (Akemann and Knopfel, 2006). The hiPSC-GN and *in silico* Purkinje neuron were designated as pre-synaptic and post-synaptic, respectively. Electrophysiological recordings were performed using the whole-cell ruptured patch clamp configuration (700B Multiclamp amplifier, Molecular Devices). Given that hiPSC-GNs typically have a depolarized resting membrane potential (RMP), we used our dynamic clamp system to virtually express a background K^+ current (I_{GHK}) to drive the RMP to more physiological values, allowing for the recording of evoked action potentials (APs). Normally, the *in silico* Purkinje neuron spontaneously fires APs. To prevent spontaneous AP firing, we virtually expressed an additional linear K^+ current (E_{rev}=-70 mV) to hyperpolarize the RMP, resulting in the requirement of a stimulating current to evoke AP firing. hiPSC-GNs were stimulated (0.8-1 nA for 1 ms, 1 Hz) resulting in AP firing (RMP = -58±2 mV, amp. = 84±6 mV, APD90 = 13.7±2.8 ms, n=6). Using Cell to Cell Mode, the hiPSC-GN voltage was used to calculate a stimulatory synaptic current (I_{STIM} = abs(voltage+60)*1.9, max. of 154 pA) for input into the *in silico* Purkinje neuron. With Cell to Cell Mode turned off (no synaptic connection), no AP firing was observed in the *in silico* Purkinje neuron. Turning on Cell to Cell mode (neurons synapsed), evoked AP firing in the hiPSC-GN resulted in AP firing in the *in silico* Purkinje neuron (RMP=-64±2 mV, amp=105±4 mV, APD_{90}=2.2±0.2 ms, n=4). We will expand on these initial studies to demonstrate the usefulness of dynamic clamp in studying neural networks such as simulating inhibitory synaptic connections and to couple multiple *in silico* neurons to the hiPSC-GNs. Synapsing real neurons to one or more *in silico* neurons will expand neuroscientists' ability to study neuronal circuits. These studies were supported, in part, by NIH NS011613, 1R43NS125749 and 5R44MH119842 grants.

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Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.01/B114

Topic: B.08. Epilepsy

Support: Hong Kong Research Grants Council, General Research Fund: 11101215, 11103220, 11101818, 11102417, 11166316, 14117319
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National Natural Science Foundation of China: 31671102
Key-Area Research and Development Program of Guangdong Province: 2018B030340001

Title: Chemogenetic suppression of the entorhinal cortex alleviates seizure severity in an acute mice model of temporal lobe epilepsy

Authors: *S. T. BELLO[1,2], J. HE[2,3];
[1]Ctr. for Regenerative Med. and Health, Hong Kong Inst. of Sci. and Innovation, Chinese, New Territories, China; [2]Dept. of Neurosci., [3]Dept. of Biomed. Sci., City Univ. of Hong Kong, Kowloon, Hong Kong

Abstract: Epilepsy is a neurological disease that is characterized by recurrent and spontaneous seizures. Hyperexcitability and hypersynchronous discharge of a population of neurons within a micro or macro-circuit results in seizure generation. On a global scale, epilepsy affects over 45.9 million people. Temporal lobe epilepsy (TLE) is the most common form of acquired epilepsy and is often characterized by hippocampal sclerosis. Epileptic activities in TLE have been attributed to the hippocampus, and the contributions of other brain areas in the temporal lobe, especially the entorhinal cortex (EC), are often neglected. In this study, we investigated how the EC participates in secondary seizure generalization in acute TLE. We hypothesize that suppressing this relay center (EC) can mitigate seizure generalization to the neocortex. TLE was induced through intrahippocampal kainic acid (IHC-KA) injection in the dorsal hippocampus of C57BL/6J mice. Neuronal network activation of the EC, neocortex, and hippocampus at 3 hours and 8 hours after IHC-KA injection, was evaluated using c-Fos staining. The population activity of EC neurons was assessed using electrophysiological recording and fiber photometry. We further adopted chemogenetic manipulation to silence EC's neuronal activities, and the resultant change in c-Fos expression and behavioral seizure were assessed. Our results revealed that the expression of c-Fos in the hippocampus, EC, and neocortex after epilepsy induction follows a time course, with c-Fos expression in the EC and neocortex reaching a peak 8 hours after IHC-KA injection indicating a longer stimulation period of the relay center (EC). Meanwhile, the

hippocampal c-Fos already peaked at 3 hours. Electrophysiological recordings of the EC's population activity showed that both epileptic spike frequency and local field potential power were increased after IHC-KA injection. In addition, the EC also showed significantly increased calcium dynamics, including the frequency of calcium peaks and mean amplitude at a population scale from fiber photometry recording after IHC-KA injection. Being a relay center, we found that chemogenetic silencing of the EC suppresses both EC and neocortical c-Fos expression without significantly affecting hippocampal c-Fos expression. Most importantly, assessment of the behavioral seizures following the chemogenetic suppression of the EC in IHC-KA injected mice further revealed a significant decrease in convulsive seizure frequency. Therefore, this study offers a new understanding of the role of EC in secondary seizure generalization and demonstrates a novel treatment strategy for TLE.

Disclosures: S.T. Bello: None. **J. He:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.02/B115

Topic: B.08. Epilepsy

Support: NYSTEM CO29155
NIH S10OD018516
Cornell Einhorn Discovery Grant
Cornell Undergraduate Research Grant

Title: Identification of Seizure-Sensitive Neurons in Drosophila Using a Novel Neural Activity-Dependent Reporter System

Authors: *X. MEI, D. L. DEITCHER;
Neurobio. and Behavior, Cornell Univ., Ithaca, NY

Abstract: *Drosophila melanogaster* has long been used as a model for epilepsy, and mutations in the gene *julius seizure* (*jus*) result in a bang-sensitive seizure phenotype (Horne *et al.* 2017). While Jus protein is expressed in selected neurons during development, it is not known if these jus-expressing neurons participate in the actual seizure when *jus* is mutated or if these neurons alter the activity of other neurons to promote seizures. We demonstrated the efficacy of a novel reporter that utilizes the transgenically expressed human ribosomal protein S6, which is selectively phosphorylated in active neurons. Given that there were no established methods to trigger seizure on larva, we developed a 10 °C cold shock behavioral assay to induce and quantify seizures on the third instar larva, and we found a corresponding increase in the level of phosphorylated S6 (pS6) 15 minutes after cold shock through immunostaining. Larva of *w[1118]; jus^{GFSTF}Tub-hS6*, a *jus* mutant line containing both the human S6 transgene and mislocalized GFP-tagged Jus protein, exhibited significantly longer seizure than *w[1118]*

(112.76s ± 34.01s vs. 40.52s ± 12.79s, n=20). Similarly, a significant increase in pS6 level was observed in Jus+ neurons in the ventral nerve cord (VNC) of this genotype following the cold shock (n=10), confirming the involvement of Jus+ neurons in temperature shock induced seizures. We also found a strong suppressive effect on the seizure phenotype when feeding larva or adult *jus* mutants with a diet supplemented with 2% - 8% whey (wt/vol), with seizure duration dropped from 112.76s ± 34.01s in jus^{GFSTF} *Tub-hS6* third instar larva on normal food to 66.66s ± 21.62s on 4% whey (n=20). Through the pS6 reporter system, we identified seizure-sensitive neurons in the VNC including Jus+ neurons that were affected by the dietary supplementation of whey. Our findings suggested the utility of the pS6 system in the functional mapping of active neurons in *Drosophila* and the potential of whey as a treatment for epilepsy.

Disclosures: X. Mei: None. **D.L. Deitcher:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.03/

Topic: B.08. Epilepsy

Support: US Department of Defence grant W81XWH-21-1-0927 (IA)

Title: Multimodal in vivo imaging of neuroinflammation and behavioural assessment in a rat model of post traumatic epilepsy

Authors: *M. JAVALGEKAR[1], N. C. JONES[1], D. WRIGHT[2];
[1]Dept. of Neurosci., Monash Univ., Melbourne, Australia; [2]Central Clin. Sch., Melbourne, Australia

Abstract: Rationale: Literature indicates that neuroinflammation could contribute to posttraumatic epilepsy and behavioural impairment following traumatic brain injury (TBI). To establish whether neuroinflammation may also represent a predictive biomarker, we longitudinally assessed Position Emission Tomography (PET) and Magnetic Resonance Spectroscopy (MRS) markers of neuroinflammation, including translocator protein (TSPO) and myoinositol (MI), after experimental TBI in rats. We then assessed whether these outcomes related to the epileptogenic and neurobehavioral impairments post TBI.
Methods: TBI (n=22) was induced by fluid percussion injury in Sprague-Dawley rats. Sham rats (n=8) underwent a craniotomy only. At 1-week and 1-month post-injury, TSPO binding was measured using a 60 min static PET scan after iv infusion of the radiotracer [^{18}F]-FBR followed by a CT scan for attenuation correction. Levels of brain MI were measured using an MRI PRESS sequence at 9.4T. At 5 months post-TBI, Morris water maze test was performed to assess the cognitive behaviour.
Results:A significant upregulation of TSPO binding was observed in the injured cortex of TBI rats compared to sham rats at 1-week post-TBI (p= 0.0071), which remained elevated at 1-month

(p= 0.0047). Enhanced TSPO binding was also observed in the hippocampus at 1 month (p=0.0036), and in the thalamus at 1-week (p= 0.0216) and 1-month (p< 0.0001). MI was significantly elevated in the perilesional cortex at 1-month (p= 0.0009), and in the thalamus at 1-week (p= 0.0287) and 1-month (p= 0.0041) time points. In the Morris water maze test, TBI animals took significantly longer to locate the platform (p< 0.0001) and exhibited fewer platform entries (p< 0.0353) as compared to sham animals, indicating cognitive impairment. TSPO expression (r^2= 0.3550, p= 0.0034) and MI levels (r^2= 0.5127, p= 0.0002) in the thalamus of TBI rats were significantly negatively correlated with spatial learning and memory at the 1-month time point.
Conclusion: TSPO binding and MI levels assessed using PET and MRS *in vivo* were acutely increased in rat brains at 1-week post-TBI and remained elevated until 1-month post-TBI, indicating sustained microglial and astrocytic activation. Increased neuroinflammation at 1-month post-TBI correlated with spatial learning deficits in TBI rats. Therefore, measuring neuroinflammation via imaging techniques could be a predictive biomarker for neurobehavioural impairments post-TBI. Ongoing work is focused on investigating the potential of these biomarkers to predict post-traumatic epilepsy.

Disclosures: **M. Javalgekar:** None. **N.C. Jones:** None. **D. Wright:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.04/B116

Topic: B.08. Epilepsy

Title: Epilepsy, brain, core temperature, stomach, heart, and breathing rhythms

Authors: *C. BERNARD[1], A. GHESTEM[2], M. N. POMPILI[3];
[1]INSERM U1106, Marseille cedex 05, France; [2]Inst. de Neurosciences des Systèmes, AMU INSERM U1106 INS, Marseille, France; [3]CIRB Col. De France, Paris, France

Abstract: Seizures display clear circadian and multidien (multiple days) cycles in most patients with epilepsy and experimental models. If circadian rhythms are well established in peripheral organs, nothing is known regarding multidien rhythms. Here, we show how central and peripheral rhythmic activities are coordinated and their relationship to seizure occurrence and interictal spike activities.We recorded the EEG, heart activity, breathing, gastric activity, and core temperature 24/7 during at least 2 months in six rats with spontaneous seizures (pilocarpine models). All modalities displayed strong circadian and multidien rhythms. Preliminary analyses indicate that interictal spikes, core temperature, heartbeat frequency, and gastric activity belong to the same oscillatory system, suggesting a common driver. Interestingly, specific changes in some modalities occur one hour before spontaneous seizures in some animals.Combining different modalities may improve the detection of high and low seizure risk periods.

Disclosures: **C. Bernard:** None. **A. Ghestem:** None. **M.N. Pompili:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.05/B117

Topic: B.08. Epilepsy

Support: NIH Grant R21NS116546
DOD Grant HT9425-23-1-0200

Title: Differential seizure susceptibility to kainic acid and differences in interictal spike wave forms in epilepsy-resistant (C57BL/6) and epilepsy susceptible (DBA) mice

Authors: *A. L. GOFORTH[1], P. YANG[2], A. GOPAL[3], D. LASKY[5], R. MAGANTI[4], M. V. JONES[6];
[1]Neurol., Univ. of Wisconsin - Madison, Madison, WI; [2]Cornell Univ., ITHACA, NY; [4]Neurol., [3]Univ. of Wisconsin-Madison, Madison, WI; [5]Neurosci., Univ. of California, Davis, Davis, CA; [6]Dept Neurosci., Univ. of Wisconsin Madison, Madison, WI

Abstract: Seizure susceptibility can vary in different mouse strains and there is currently no way to predict who develops epilepsy following a CNS insult, just as in humans. We previously showed that interictal spikes (IIS) in the EEG differ in their shapes between saline (SA) treated mice and those that experienced an epileptogenic insult (kainic acid, KA). Here, we further explore the relations between IIS waveform shapes and the risk of epilepsy, in epilepsy-resistant (C57) and epilepsy-susceptible (DBA) mice. We collected EEG data from 12-week-old C57BL/6 and DBA mice for 8 weeks following repeated low dose KA (C57s n=8; DBAs n=6) or SA (C57s n=7; DBAs n=4) treatments. Spontaneous seizures were manually scored. EEG records from week-3 EEG post injection were subjected to an automated spike detection algorithm (doi: 10.1371/journal.pone.0207158). We employed Bayesian statistics to determine the probability of an animal being epileptic based on the features of the IIS. Finally, differences in IIS features between mice that did or did not develop epilepsy post-KA were also examined. Spontaneous seizures were seen in 3/8 KA-treated C57s and 5/6 KA-treated DBAs starting in week 2. Mean weekly seizure frequency across weeks 2-8 after KA treatment was 9.4±5.06 (Range: 1-17) in C57s whereas it was 24.7±9.0 (Range: 11-38) in DBAs ($p<0.05$). The average number of spike waveforms detected per animal in each group in a 1-day recording by the spike detection algorithm was 524 ± 221 in C57+KA group, 61 ± 14 in C57+SA group; 360 ± 110 in DBA+KA and 318 ± 120 in DBA+SA group. Using Principal Components Analysis (PCA), we found that spike waveforms formed "clouds" in PCA space where IIS from SA-treated C57 and DBA mice fell in a blob together. In contrast, IIS from KA mice tended to fall in "arms", separate from the main cluster. These "clouds" of data points (i.e., waveform shapes) in PCA space can be viewed as probability densities. The Bayesian posterior probability that an IIS waveform belonged to an animal that ultimately developed epilepsy, was 0.67 in C57s and 0.76 in DBAs. Therefore,

quantification and analysis of IIS waveforms during the latent period may be useful in predicting future epilepsy. Spikes in C57s and DBAs that developed epilepsy had different waveforms than spikes in SA mice, with a higher amplitude and a pronounced after-following slow-wave. Spikes in KA animals that did not develop epilepsy did not differ from those with SA treatment Our data confirmed that DBA mice are more epilepsy-susceptible than C57 mice, with greater seizure frequency. PCA analysis showed that IIS waveforms were different in animals destined to develop epilepsy compared to those that were not.

Disclosures: A.L. Goforth: None. **P. Yang:** None. **A. Gopal:** None. **D. Lasky:** None. **R. Maganti:** None. **M.V. Jones:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.06/B118

Topic: B.08. Epilepsy

Support: NIH R01NS126594
UVA Wagner Fellowship
The Ingrassia Family Echols Scholars Research Fund
UVA Double Hoo Award

Title: Brain-wide single-unit activity during spike-wave discharges

Authors: *E. DULKO[1], A. CARNS[1], S. KILIANSKI[2], M. PIKUS[1], M. P. BEENHAKKER[2]; [2]Pharmacol., [1]Univ. of Virginia, Charlottesville, VA

Abstract: Title: Brain-wide single-unit activity during spike-wave discharges
Background: The spike-wave discharge (SWD) is the hallmark of Absence Epilepsy (AE), a disease that affects up to 8 per 100,000 children under 15 years of age. Currently available anti-seizure medications reduce seizure occurrence but are associated with unacceptable freedom from treatment failure rates (~50%) due to intolerable side effects. Understanding the neuronal mechanisms of SWD generation is a necessary step for developing better, targeted treatments. Prior research suggested that SWDs are driven by hypersynchronous neural circuits of the cortex and thalamus. However, beyond this general conclusion, many significant questions remain, and little is known about neuronal activity underlying seizure generation. **Methods:** 24 C3H/HeJ ("Gria4") mice, a common model of spontaneous SWDs were used in this study. Using simultaneous single-unit and electrocorticographic (ECoG) recordings in head-fixed mice, we examined firing of ~1,000 individual neurons across 20 brain structures including somatosensory cortex, most thalamic nuclei, and hippocampus. **Results:** We found that most brain structures are recruited during the SWD and fire sparsely but synchronously during each cycle of the SWD. Moreover, phase-analysis revealed that temporal firing pattern is modulated by SWD and consistent between mice. We also found that within and between brain structures synchrony

increases 3.5-fold and 2-fold compared to the baseline, respectively during SWDs. We resolved the lag between brain structures and identified the leading and following brain structures. The results of this study - a single-unit resolution activity map driving during the SWD - is an essential first step for the development of novel therapeutic strategies for a common childhood form of epilepsy associated with unacceptable failure rates.

Disclosures: **E. Dulko:** None. **A. Carns:** None. **S. Kilianski:** None. **M. Pikus:** None. **M.P. Beenhakker:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.07/B119

Topic: B.08. Epilepsy

Title: Development and application of a machine learning-based digital biomarker to detect lateral position associated with spontaneous seizures in preclinical epilepsy models

Authors: J. M. LEEDY[1], ***N. E. PELTIER**[3], B. BERRIDGE[4], N. BRATCHER-PETERSEN[5], M. ELLIS[6], T. ROBERTSON[3], M. RUIDIAZ[3], M. C. SAUL[7], M. LOPEZ[2];
[1]BioMarin Pharmaceut. Inc., Petaluma, CA; [2]BioMarin Pharmaceut. Inc., San Rafael, CA; [3]TLR Ventures, Redwood City, CA; [4]B2 Pathology Solutions LLC, Cary, NC; [5]DIVA/TLR Ventures, Redwood City, CA; [7]Data Sci., [6]The Jackson Lab., Bar Harbor, ME

Abstract: Epilepsy is a chronic neurological disorder characterized by seizures and periods of unusual behaviors that affects an estimated 50 million people worldwide. Rodent models of epilepsy are essential for understanding underlying mechanisms of the disorder and developing novel therapeutics. The gold standard assay to monitor for spontaneous seizures in rodent models of epilepsy is video/ electroencephalography (vEEG). vEEG in animals is low throughput, requiring specialized data acquisition systems, surgical implantation of electrodes, and expert data analysis. For these reasons, the field is often limited in its ability to fully characterize spontaneous seizure dynamics across a growing number of preclinical epilepsy models.
This work demonstrates advances in the development of automated detection of seizures of individual animals in group-housed mice. Continuous, objective, and quantitative assessment of defined behaviors was done using machine learning-enabled algorithms applied in real time to raw computer vision video. For development of a lateral position measure, mice were treated with pentylenetetrazol (PTZ). The model was further developed using a natural history characterization of two mouse models of Dravet Syndrome, a severe genetic epileptic encephalopathy, characterized by spontaneous tonic-clonic seizures and SUDEP over the early course disease. Furthermore, we demonstrate how digital biomarkers allow for multiplexing of phenotypic readouts, assessing the interplay between seizure, activity metrics, sleep wake cycle, etc. concurrently in the same cohort of mice. The ability to noninvasively detect lateral position due to loss of righting in the home cage in real time offers value for health and welfare

monitoring. The non-invasive nature of digital home cage monitoring also enhances the efficiency of spontaneous seizure detection and offers significant value in development models that are more translationally relevant and reproducible. This data emphasizes the potential wide-ranging impacts of this technology in preclinical epilepsy research and beyond.

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Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.08/Web Only

Topic: B.08. Epilepsy

Support: CONAHCYT 1133116
BUAP-CA-288

Title: The effect of allopregnanolone on absence seizures in the taiep rat.

Authors: *E. A. ROJAS, Jr.[1,2], J. R. EGUIBAR, Sr.[3], C. CORTES, Sra.[4];
[1]Inst. of physiology, BUAP, Puebla, Mexico; [2]Inst. of physiology, Benemérita Univ. Autónoma de Puebla, Puebla, Mexico; [3]Behavioral Neurophysiol., Benemerita Univ. Autonoma De Puebla, Puebla, Mexico; [4]Inst. of Physiol., B. Univ. Autonoma de Puebla, Puebla, Mexico

Abstract: The *taiep* rat is an animal model with a mutation in the beta-4A tubulin gene, which is the only animal model of the human leukodystrophy hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC). *Taiep* rats had a spike-wave discharges (SWDs) on the electroencephalogram (EEG) with a main frequency of 6.25 Hz. Additionally, we demonstrated a sexual dimorphism in the expression of SWDs being males more affected than adult female *taiep* rats. Sex hormones such as progesterone and its derivative allopregnanolone could play a key role in the incidence of SWDs. This study was aimed to determine the effect of allopregnanolone on SWDs in adult *female taiep* rats. A 6-month-old female *taiep* rats were implanted with electrodes in the cerebral cortex for EEG recordings and an electromyography (EMG) and electrooculogram (EOG) electrodes with stereotactic surgery under deep halothane anesthesia. We did two EEG recordings with a duration of 12 hours, the first control with 0.2 mL olive oil subcutaneously (s.c.) administration and the second with 10 mg of allopregnanolone. Our results shown that allopregnanolone significantly increased both the frequency of SWDs (75%) and their mean duration (74%) with respect to control conditions. These results support that allopregnanolone through the modulation of GABAa receptors is capable to worsen the expression of SWDs in *taiep* rats and maybe in patients with H-ABC or with other leukodystrophies.

Disclosures: **E.A. Rojas:** None. **J.R. Eguibar:** None. **C. Cortes:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.09/B120

Topic: B.08. Epilepsy

Support: R01NS129722 (GFB)
F31NS125955 (KGJ)
T32NS007421 (MJS)

Title: Assessing effects of seizures on dorsal raphe serotonergic neuronal activity

Authors: *M. J. SUMMERFIELD[1,2], M. N. MOQUETE[3], K. G. JOYAL[3], G. F. BUCHANAN[3];
[1]Univ. of Iowa, Iowa City, IA; [2]Neurology, University of Iowa, Iowa City, IA; [3]Neurol., Univ. of Iowa, Iowa City, IA

Abstract: Epilepsy effects more than 65 million people worldwide. One-third of this population will be refractory to anti-seizure drugs. These patients are at increased risk for sudden unexpected death in epilepsy (SUDEP). The mechanisms that cause SUDEP are not well understood. A potential mechanism is impaired arousal postictally. Our lab has previous demonstrated that dorsal raphe nucleus (DRN) serotonin (5-HT) neurons are involved in CO_2 arousal, and this chemosensitivity is impaired when these neurons are absent. We investigated the effect a seizure has on DRN 5-HT neuronal activity to evaluate whether these neurons are negatively impacted, thus impairing their CO_2 chemosensitivity. We hypothesized that following a seizure, DRN 5-HT neuronal activity is refractory compared to baseline and unresponsive to inspired CO_2. To measure DRN 5-HT neuronal activity, we utilized Fiber Photometry to recording Ca^{2+} activity as proxy of neuronal activity. Male and female (8-10 wks) Pet1-Cre mice and Pet1-Cre::GCaMP mice were used in this study. The Pet1-Cre mice express Cre recombinase under a Pet1 promoter. The Pet1::GCaMP mice are a cross between the Pet1-Cre mice and Ai96(RCL-GCaMP6s) mice, which conditionally express fluorescent Ca^{2+} indicator GCaMP6s. Pet1-Cre mice were injected with Cre conditional AAV1-GCaMP6s in to the DRN (AP: -4.60, ML: ±0.0, DV: -2.93), allowing for Cre dependent expression of GCaMP6s. Both lines were instrumented with EEG and EMG electrodes, photometry fibers in the DRN, and bipolar electrodes into the amygdala for kindling (AP: -1.34, ML: -2.80, DV: -4.70). Both lines were subjected to the amygdala kindling procedure to evoke electrically induced seizures. Mice were placed in plethysmography chambers and Ca^{2+} signaling was recorded during the trial. Room air (21% O_2 / bal N_2) was administered during baseline recording, a seizure was induced, and the mouse was either given a CO_2 (7% CO_2 / 21% O_2 / bal N_2) challenge or switched to another room air tank. Pet1-cre and Pet1::GCaMP mice both display increased DRN 5-HT neuronal activity just prior to CO_2 arousal. However, this activity is impaired postictally in both lines. For the Pet1-Cre line, there was no response to CO_2 for a duration after the seizure ends. The Pet1::GCaMP line displayed similar impairment. Such findings support that seizures negatively

impact the neurons that contribute to CO_2 arousal. Recording from the DRN 5-HT demonstrated a refractory period following electrically induced seizures. Future directions include examining the DRN 5-HT projections and identifying subservient CO_2 chemoreceptive populations.

Disclosures: M.J. Summerfield: None. **M.N. Moquete:** None. **K.G. Joyal:** None. **G.F. Buchanan:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.10/B121

Topic: B.08. Epilepsy

Support: DA040621

Title: ΔFosb disulfide bond formation in vivo affects neuronal gene expression and behavior

Authors: *D. ANDERSON[1], B. HUGHES[2], E. J. NESTLER[3], A. ROBISON[1];
[1]Michigan State Univ., East Lansing, MI; [2]Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Epilepsy is a chronic neurological disorder diagnosed in about seventy million patients globally. It involves spontaneous recurrent seizures caused by an upsurge in hyperexcitability of neurons throughout the brain, often originating in the hippocampus. During seizures, the hippocampus dramatically upregulates expression of ΔFOSB, an immediate early gene transcription factor with a remarkable half-life of 8 days in the brain. Our research indicates that activity-dependent accumulation of ΔFOSB reduces excitability of glutamatergic hippocampal pyramidal cells, potentially serving as a mechanism to counteract hyperexcitability and seizures. In support of this, mice lacking the *FosB* gene have spontaneous seizures and malformation of the hippocampus, and thus the ΔFOSB AP1 complex emerges as a promising druggable target for potential therapeutic interventions in epilepsy treatment. Moreover, under redox stress ΔFOSB can form disulfide bonds at residue C172 with JunD, its obligate binding partner, and these bonds can alter the ability of ΔFOSB to bind DNA in vitro and in cultured cells. Our lab has developed a new transgenic mouse line harboring a C172S point mutation, as well as a separate full *FosB* KO mouse. These transgenic tools will allow us to determine the role of ΔFOSB and C172 disulfide bond formation in seizures as well as in other key behaviors regulated by ΔFOSB like drug responses, mood, and learning. We used an array of behavioral assays to measure anxiety-like behavior, anhedonia, locomotor activity, reward-seeking, drug responses, and learning and memory. We also characterized the susceptibility of these mice to pilocarpine-induced seizures. We then treated mice with potassium dichromate, an oxidative agent that causes redox stress in the brain. Western blots were conducted to measure levels of ΔFOSB in key brain regions, and CUT&RUN was used to measure binding of ΔFOSB to target

genes. Identification mechanisms of ΔFOSB function under oxidative stress could be beneficial for treatment of epilepsy, addiction, among other brain disorders.

Disclosures: D. Anderson: None. **B. Hughes:** None. **E.J. Nestler:** None. **A. Robison:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.11/B122

Topic: B.08. Epilepsy

Title: Utilizing rat kindling models (amygdala and hippocampal) for anti-epileptic drugs (AEDs) screening

Authors: *S. ZHONG[1], L. KRETSGE[1], C. H. RUEDA[2], H. LI[1], S. RAMBOZ[3], A. GHAVAMI[4];
[1]PsychoGenics INC, Paramus, NJ; [2]Pharmacol., PsychoGenics INC, Paramus, NJ; [3]Neurodegeneration, PsychoGenics, Paramus, NJ; [4]PsychoGenics, Paramus, NJ

Abstract: Kindling model in rodent is a progressive model causing permanent increase in seizure susceptibility and a reliable model to screen for anti-epileptic drug (AEDs) (Loscher and Honack, 1993; Klitgaard et al., 1998). Rodent can be either hippocampus or amygdala-kindled. To do so electrodes were stereotaxically implanted into the basolateral amygdala (or ventral Hippocampus) of rats for stimulation and local field potential (LFP) recording. A surface electrode (screw electrode) was also implanted into the skull above the motor cortex for EEG recording. The seizure severity of the rat's responsive behavior (Racine's 5 stage scale) was graded online, and video recorded. Simultaneity, after discharge (AD) of EEG and deep brain LFP were collected for offline analysis. In this current study, we have used three reference compounds including Levetiracetam showing robust anti-seizure effect in chronic and rapid kindling procedures in both rat hippocampus and amygdala were used for the study.

Disclosures: S. Zhong: None. **L. Kretsge:** None. **C.H. Rueda:** None. **H. Li:** None. **S. Ramboz:** None. **A. Ghavami:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.12/B123

Topic: B.08. Epilepsy

Support: NIH NINDS 2R01 NS100019
NIH NINDS 1RF1AG083625-01

Title: Apoe4 and seizure susceptibility in alzheimer's disease

Authors: *K. LIM[1], H. CHUNG[2];
[1]Univ. of Illinois, Urbana-Champaign, Savoy, IL; [2]Dept Mol. and Integrative Physiol., Univ. of Illinois At Urbana Champaign, Urbana, IL

Abstract: Alzheimer's Disease (AD) is the leading cause of dementia. While hyperphosphorylated tau is well correlated with neurodegeneration and cognitive deficits in AD, APOE4 is the strongest genetic risk factor for late-onset AD and causes age-dependent seizures in mice. Here we tested whether seizure susceptibility is increased by APOE4 and hyperphosphorylated tau, and if such increase can by blocked by a small molecule PH002 which is previously shown to convert APOE4 to a normal APOE3-like structure *in vitro*. We induced seizures in human APOE4 or APOE3 knock-in mice (hAPOE4, hAPOE3) and PS19 tauopathy mouse model by the chemoconvulsant kainic acid (KA) which potently activates the hippocampus. At high-dose KA (30 mg/kg, i.p), hAPOE4 mice of both sexes showed increased seizure severity and mortality compared to hAPOE3 and PS19 mice at 5-7 but not in 2-3 months of age. At low-dose KA (15 mg/kg, i.p), hAPOE4 worsened seizures only in female PS19 mice. Furthermore, there was a decreasing trend in KA-induced mortality in hAPOE4 mice when compared to APOE3 mice after PH002 treatment for 6 weeks. This study demonstrates that hAPOE4 induces age-dependent hippocampal hyperexcitability, and exacerbates seizure propensity in the tauopathy models.

Disclosures: K. Lim: None. **H. Chung:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: B.08. Epilepsy

Support: NIH Grant R21 NS112948
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NIH Grant S10 OD021773
NIH Fellowship F31 NS115479
The Mirowski Family Foundation

Title: Cortical spreading depolarization after seizure is associated with depletion of endoplasmic reticular calcium

Authors: *K. BERGLUND, M. A. STERN, E. COLE, C.-A. N. E. GUTEKUNST, R. E. GROSS;
Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Cortical spreading depolarization (CSD) has been observed to follow seizures and has been shown to have a seizure-suppressive effect. While cells during both seizures and CSD experience increases in intracellular calcium, they may be mediated by distinct molecular signals. Understanding of intracellular signaling during seizures and CSD could offer insight to better understand anti-epileptic effect of CSD. To explore calcium signaling during these events, we performed simultaneous two-photon calcium imaging of the cytosol and ER lumen in awake mice during pentylenetetrazol induced seizures and electrically induced CSD. Electroencephalogram (EEG) and direct-current (DC) potential were concurrently recorded to independently monitor ictal activity and CSD, respectively. In the cytosol, CSD appeared as slow-propagating calcium waves after seizure. A depletion of ER calcium stores was observed during CSD but not during seizure. We determined precise timing of the increase of cytosolic calcium and the decrease of ER calcium in individual neurons, consistent with a calcium induced calcium release. When CSD followed a seizure, post-ictal activity decreased, further implicating the role of CSD in suppressing ictal activity.

Disclosures: K. Berglund: None. **M.A. Stern:** None. **E. Cole:** None. **C.N.E. Gutekunst:** None. **R.E. Gross:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.14/B125

Topic: B.08. Epilepsy

Support: NIH Grant R01 NS128222-01A1

Title: Layer-specific excitatory inputs differentially contribute to interictal spikes in the dentate gyrus

Authors: *J. D. YI[1], G. TARCSAY[2], N. MASALA[3], B. L. BOUBLIL[3], L. A. EWELL[2];
[1]Univ. of California, Irvine, Irvine, CA; [2]Anat. & Neurobio., Univ. of California, Irvine, Irvine, CA; [3]Anat. and Neurobio., Univ. of California, Irvine, Irvine, CA

Abstract: Temporal lobe epilepsy (TLE) is associated with hippocampal sclerosis characterized by cell loss & gliosis in multiple hippocampal subfields and granule cell dispersion (GCD) in the dentate gyrus (DG). The supra-hippocampal kainic acid (KA) model of TLE in mice recapitulates these histopathological findings and provides an accessible system for studying epileptiform activity. We seek to understand circuit mechanisms of interictal spikes (IS), which are believed to be prognostic of seizure risk. It is hypothesized that pro-excitatory changes, like sprouted mossy fibers, seen in the otherwise sparsely active DG destroy a “gate” which usually

protects against excess excitation delivered to the hippocampus via the entorhinal cortex (EC). We hypothesize that ISs provide a window into how the gate may transiently break down. To test this hypothesis, we examined the local field potential (LFP) of the DG using chronically implanted high-density neural probes in freely moving KA-injected (N = 2) & KA-naïve mice (N = 1) during rest. Dentate spikes (DS) were detected and clustered to locate current sinks in the putative middle- or outer-molecular layers (MML/OML). These DS sinks served as proxies for EC excitatory projection activity. For TLE mice with DS, their ML sinks were separated by around 1000 μm, as opposed to approximately 300 μm in the control mouse, consistent with the histological expansion we observed due to granule cell dispersion. By contrast, ISs, which occurred at a rate of around 8/min, had sustained sinks in the putative inner molecular and granule cell layers. Interestingly, 25-100 ms before the IS peak, the largest magnitude current sink (if present) occurred in the territory of the presumptive MML. We confirmed these large sinks significantly resembled those of DSs by comparing the current sink spatial profile of DS to that of a given IS using cosine distance ($p < 10^{-8}$, bootstrapped against a null distribution of scrambled DS templates). Taken together, these preliminary findings suggest that in TLE mice, EC input is integrated in analogous layer-specific locations along the dispersed granule cell dendritic tree. Furthermore, ISs are sustained by recurrent mossy fibers which synapse more proximal to the granule cell bodies than the putative EC input. These spatial patterns are consistent with reported anatomical data on the distributions of EC & sprouted mossy fiber synapses observed in similar epilepsy models. Finally, presumptive excitatory drive from the EC can precede epileptiform spikes, hinting at a tentative culprit overloading the DG "gate" in TLE.

Disclosures: **J.D. Yi:** None. **G. Tarcsay:** None. **N. Masala:** None. **B.L. Boublil:** None. **L.A. Ewell:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.15/B126

Topic: B.08. Epilepsy

Support: NIH R01 NS128222-01A1

Title: Hippocampal representation of a new environment in a rodent model of temporal lobe epilepsy

Authors: *B. L. BOUBLIL[1], G. TARCSAY[1], L. A. EWELL[1,2];
[1]Anat. and Neurobio., UC Irvine, Irvine, CA; [2]Center for the Neurobiology of Learning and Memory, UC Irvine, Irvine, CA

Abstract: Place representation in the hippocampus is disrupted in animal models of TLE. Much of the research on the hippocampus in epilepsy has focused on CA1, and little is known about how the function of upstream regions such as CA3 and DG may be altered in epilepsy. We

performed high density single-unit recordings from all subregions in epileptic and saline control mice. Mice were trained to forage in a familiar environment while tetrodes were slowly advanced towards all subregions. Once tetrodes reached their target, we recorded hippocampal neural activity while mice explored both familiar and novel environments (N = 9, 4 control, 5 epileptic). In control mice, we observe a trend toward spatial remapping of CA3 fields between a familiar and novel environment ($p = 0.058$), which was accompanied by a rate change ($p = 0.057$). In epileptic mice, we also observed remapping of CA3 place fields ($p = 0.028$), however, we observed no rate change, indicating impaired rate mapping in new environments (n.s., $p = 0.421$). The rate change in control mice was significantly larger than in mice with epilepsy ($p = 0.032$). Current analyses are underway to assess additional features of spatial coding, such as spatial information and field size, as well as place field development and stabilization with experience in novel environments. By better understanding CA3 dynamics and how they change with epilepsy we can gain insight into impaired memory processing in epilepsy.

Disclosures: **B.L. Boublil:** None. **G. Tarcsay:** None. **L.A. Ewell:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.16/B127

Topic: B.08. Epilepsy

Support: JPB Foundation
Picower Institute for Learning and Memory
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R01 NS123120
Swiss National Science Foundation
Swiss Neurological Society

Title: Low-current thalamic deep brain stimulation induces spike-wave discharges in mice

Authors: *F. J. FLORES[1,2,3,4], I. DALLA BETTA[5,6], J. TAUBER[7], D. R. SCHREIER[1,8,9,10], E. P. STEPHEN[7], M. A. WILSON[5,4], E. N. BROWN[1,2,3,4,11];
[1]Anesthesia, Critical Care, and Pain Med., Massachusetts Gen. Hosp., Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA; [4]Center for Brains, Minds, and Machines, Massachusetts Institute of Technology, Cambridge, MA; [5]Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [6]Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA; [7]Mathematics and Statistics, Boston Univ., Boston, MA; [8]Neurology, Bern University Hospital, Bern, Switzerland; [9]University of Bern, Bern, Switzerland; [10]Neurology, Massachusetts General Hospital, Boston, MA; [11]Institute for Medical Engineering and Sciences, Massachusetts Institute of Technology, Cambridge, MA

Abstract: Deep brain stimulation of central thalamic nuclei (CT-DBS) is an effective technique for modulating states of consciousness: it has helped to speed recovery from minimally conscious states (MCS) in humans, reverse the effects of anesthesia in non-human primates (NHPs), and enhance cognitive abilities in awake rodents and NHPs. However, CT-DBS can also induce spike-wave discharges (SWDs) in cats, NHPs, and humans. SWDs are characterized by a series of spikes and waves observed in the electroencephalogram (EEG) or local field potentials, and are associated with absence seizures in humans. In this study, we implanted mice with electrodes to deliver unilateral and bilateral CT-DBS at different frequencies while recording EEG. We titrated the stimulation current required to produce an SWD at different frequencies by gradually increasing the current at each frequency until an SWD was induced. Subsequent test stimulations were performed at the current one step below the current that produced an SWD during titration. We found that 2.21% [1.46 - 3.33%] of the test stimulations caused SWDs at currents lower than the titrated current in 10 out of 12 mice, even at currents as low as 20 uA. Higher currents during tests had a higher probability of inducing an SWD, and the history of previous stimulation did not have an effect on the probability of causing an SWD. The duration of the SWDs caused by test stimulations was not significantly different from the duration of those caused by titrations stimulations. SWDs that were caused during titrations had a slightly shorter median latency from stimulation onset than SWDs caused during test stimulations. Our study found a small but significant probability of causing SWDs during CT-DBS, even after titration and at relatively low currents. EEG should be closely monitored for SWDs when performing CT-DBS in both research and clinical settings, especially when performed in awake, healthy subjects.

Disclosures: **F.J. Flores:** None. **I. Dalla Betta:** None. **J. Tauber:** None. **D.R. Schreier:** None. **E.P. Stephen:** None. **M.A. Wilson:** None. **E.N. Brown:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MASIMO. Other; PASCALL.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.17/B128

Topic: B.08. Epilepsy

Support: NIH/NINDS grant #R01-NS071785-15 (to S.C.B.).

Title: Neurobehavioral deficits and embryonic MGE progenitor transplantation in C1qa knockout mice

Authors: *J. RIGHES MARAFIGA, T. VU, J. BOWLUS, S. C. BARABAN; Neurolog. Surgery, Univ. of California, San Francisco, San Francisco, CA

Abstract: Neurobehavioral changes are often associated with brain dysfunction due to disease, injury, or toxicity. Diverse conditions such as Alzheimer's disease, epilepsy, and autism spectrum disorders are examples of neurological disorders that display disabling neurobehavioral impairments of various types. These include, but are not limited to, psychiatric, neurobehavioral, social abnormalities (e.g., anxiety, social dysfunction, attention changes), and sensory deficits. We propose that transplanting GABA progenitors derived from embryonic medial ganglionic eminence (MGE) can alter neuronal networks and neurobehavioral comorbidities including somatosensory cortical-related behaviors in healthy and disease states. Our approach includes: (1) murine embryonic MGE progenitor cell transplantation into somatosensory cortex at postnatal day 2 (n= 10 mice, male and female), (2) video-EEG and/or 32-channel *in silico* local field potential recording of transplanted mice at 60 days after transplantation (n= 4 mice per group), and (3) neurobehavioral performance evaluation using standard anxiety, sociability, and sensory behavioral assays (n= 6 mice each group). Wild-type C57BL6 mice were used as healthy recipients for MGE transplantation. C1qa KO mice (JAX:031675) presenting anxiogenic behavior and whisker-dependent behavior abnormalities (n= 6 mice) were used as absence epilepsy recipients for MGE transplantation. Here we show: (1) impaired neurobehavioral performances of C1qa KO mice during anxiety (dark/light preference) and sensory behavioral (texture novel recognition object) assays; (2) spontaneous EEG abnormalities including 1-5 Hz spike-and-wave discharge activity in C1qa KO mice; and (3) efficient migration, differentiation, and functional integration of MGE progenitor cells into somatosensory cortex of healthy control mice and C1qa KO mice. Altogether, these results highlight the potential for interneuron-based transplantation to alter neuronal networks and associated neurobehaviors in mice. Support: NIH/NINDS grant #R01-NS071785-15 (to S.C.B.).

Disclosures: **J. Righes Marafiga:** None. **T. Vu:** None. **J. Bowlus:** None. **S.C. Baraban:** None.

Poster

PSTR011: Epilepsy Models: *In Vivo* and Behavioral Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.18/B129

Topic: B.08. Epilepsy

Support: NIH Grant R21NS116546 (MVJ)
DoD PR221869 (RM)

Title: Alterations in circadian regulation of sleep state transitions in epilepsy-resistant (C57) and epilepsy-susceptible (DBA) mice.

Authors: A. GOPAL[1], P. YANG[2], D. LASKY[3], R. MAGANTI[1], ***M. V. JONES**[4];
[1]Univ. of Wisconsin-Madison, Madison, WI; [2]Cornell Univ., ITHACA, NY; [3]Neurosci., Univ. of California, Davis, Davis, CA; [4]Neurosci., Univ. of Wisconsin Madison, Madison, WI

Abstract: Epilepsy and sleep have a complex but poorly understood interrelationship. Patients with epilepsy frequently report disrupted sleep and sleep disruptions are a frequent trigger for seizures, suggesting a vicious cycle that may contribute to disease progression. Sleep is regulated via multiple mechanisms and problems with sleep regulation may be involved in epilepsy. A common form of epilepsy is acquired through an "initial insult" that causes some subjects to develop spontaneous seizures later (i.e., epilepsy). At present, there is no way to predict which individuals will develop epilepsy. Here, we investigated whether sleep statistics can serve as a potential biomarker by comparing sleep state transitions between epilepsy-resistant (C57) and epilepsy-susceptible (DBA) mouse strains, following an epileptogenic (kainic acid, KA) or a sham insult (saline, SA). We collected 24-hour EEG records from C57 and DBA mice, several weeks after either a) KA i.p. injections that caused an initial status epilepticus insult or b) sham SA injections. Mice were housed with a 12/12 hr lights on/off schedule. Sleep states were first scored manually in 4 second epochs on a subset of records. Then the Accusleep algorithm (doi:10.1371/journal.pone.0224642) was trained on that subset and, after validation against manual scoring, was used to score the remaining records. Because there were clearly two distinct Wake states, we used the following four definitions of sleep states: LongWake (LW, >=400 sec), ShortWake (SW, <400sec), NREM (N) and REM (R). State transition rate matrices (4x4) were computed in 3-hour blocks over each 24-hour EEG, yielding a trajectory for each type of transition (e.g., LW-LW, LW-N, N-SW, etc). We found that several transition types showed a circadian rhythm in both C57 and DBA control (SA) groups: i) LW-LW, ii) N-N, iii) R-R, iv) N-R and v) R-SW. The diagonal matrix elements (e.g., LW-LW, N-N, etc) illustrate "persistence" of a state, thus our data suggest that LW, N and R are all under strong circadian regulation in normal SA animals. In C57+KA, the strength of circadian modulation appeared to be increased, whereas in DBA+KA circadian modulation was severely disrupted. In summary, DBA and C57 had similar circadian regulation of sleep transitions in control conditions (SA), but differed strongly after an epileptogenic insult (KA), such that DBA (epilepsy-susceptible) mice lost circadian regulation. Our data suggest that analyses of sleep characteristics during the "latent period" may be informative about susceptibility for future epilepsy.

Disclosures: **A. Gopal:** None. **P. Yang:** None. **D. Lasky:** None. **R. Maganti:** None. **M.V. Jones:** None.

Poster

PSTR012: Alzheimer’s Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.01/B130

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

Support: AMED JP22dk0207053
JSPS KAKENHI 20K07971
JSPS KAKENHI 22K07597
JSPS KAKENHI 22K07562
JSPS KAKENHI 22K15752

JSPS KAKENHI22K15765
JSPS KAKENHI23K07016

Title: Blood RNA transcripts show changes in inflammation and lipid metabolism in Alzheimer's disease and mitochondrial function in mild cognitive impairment.

Authors: *J. IGA[1], Y. YOSHINO[2], Y. FUNAHASHI[3], S. OCHI[4], S.-I. UENO[1];
[1]Ehime Univ., Toon, Japan; [2]Neuropsychiatry, Toon, Japan; [3]Ehime Univ. Grad. Sch. of Med., Toon/Ehime, Japan; [4]Ehime Univ. Grad. Sch. of Med., Toon / Ehime, Japan

Abstract: Background: Abnormal immunity in the periphery have been reported in the pathogenesis of Alzheimer's disease (AD). **Objective**: In this study, blood transcriptome analyses of patients with AD, those with mild cognitive impairment (MCI) due to AD, and heathy controls were performed to elucidate immune-mediated pathophysiology. **Methods**: The sample included 63 subjects from complete enumeration study of elderly people in Nakayama town (the Nakayama Study), who were over 65-year-old, diagnosed as (1) healthy controls (N=21), (2) having MCI due to AD (N=20), and (3) having AD (N=21). Every subject was held with blood examination, magnetic resonance imaging, and questionnaires about lifestyles and cognitive function. With transcriptome analysis, differential gene expressions in the blood of three groups were evaluated by gene ontology, pathway enrichment, and ingenuity pathway analyses, and quantitative real time PCR was performed. **Results**: Neutrophil extracellular trap signaling was increased, and lipid metabolism (FXR/RXR activation, triacylglycerol degradation) was decreased in AD, whereas MCI showed protective responses via decreased neutrophil extracellular trap signaling and mitochondrial functions such as upregulation of the sirtuin pathway and downregulation of oxidative stress. **Conclusions**: Based on these findings, immune cells appear to have important roles in the pathogenesis of AD, and the transcriptome in blood may be useful as a biomarker for diagnosis via monitoring immunity in MCI and AD.

Disclosures: J. Iga: None. **Y. Yoshino:** None. **Y. Funahashi:** None. **S. Ochi:** None. **S. Ueno:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.02/B131

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

Support: Cure Alzheimer's Fund
Hevolution/American Federation for Aging Research
National Institute on Aging R01AG068293

Title: Spatially resolved brain region and cell type specific molecular changes in a mouse model of Alzheimer's disease

Authors: *X. SUN[1], L. WU[2], A. HECK[2], K. YOUNG[2], T. ORR[3], M. ORR[4,5];
[1]Wake Forest Sch. of Med., Winston Salem, NC; [2]NanoString Technologies (a Bruker company), Seattle, WA; [3]Dept. of Intrnl. Med. Section on Gerontology and Geriatric Med., Wake Forest Univ. Sch. of Med., Winston Salem, NC; [4]Dept. of Intrnl. Med. Section on Gerontology and Geriatric Med., Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [5]Salisbury VA Med. Ctr., Salisbury, NC

Abstract: A hallmark of Alzheimer's disease is the progressive increase in tau accumulation and its spread throughout the brain. Understanding the underlying molecular biology associated with these changes across cell types requires multi-omic spatial profiling platforms. We employed CosMx™ Spatial Molecular Imaging (SMI), a platform that supports transcriptomic analysis on intact tissue sections at subcellular resolution, to characterize these pathological dynamics. A curated panel of 1,000 RNAs was applied to coronal brain sections from the rTg4510 mouse model of tauopathy at 20 months of age. Segmentation at single-cell resolution was generated by the staining against histone, 18S rRNA, glial marker GFAP, and tau tangle marker AT8. After the validation of cell type identification, we used differential expression analysis to identify cell type specific responses to tau tangles and InSituCor method to discover cell-type independent, spatially co-expressed modules of genes.This combined approach highlighted the brain region-specific changes associated with tau pathology. In the hypothalamus, *Pomc*, *Carpt*, and *Gal*, key genes related to feeding and body weight regulation, formed spatial niches likely driven by cholinergic inhibitory neurons. In the hippocampal and cortical regions, InSituCor analysis revealed the upregulation of several gene modules related to inhibitory neuron functions. This was in agreement with the cell typing results that rTg4510 brains featured a decrease in the density of excitatory neuron subtypes and an increase in inhibitory neurons. Moreover, we previously developed a senescence eigengene approach and identified that excitatory neurons exhibit a strong senescent phenotype that coincident with tau load. We applied the same method to our data set and found that excitatory neurons had the highest average single cell score of eigengene expression. To explore their senescent signature in relation to tau load, we grouped neurons based on their distance to AT8-postive tangles (10 µm intervals for the first 50µm, then all cells >50 µm). A small portion of neurons closest to tangles (10-20 µm) exhibited elevated senescent score, as well as neurons far away (>50 µm) from tangles. These results demonstrate that themolecular responses to tau pathology are cell type and brain region dependent. Spatial profiling platform is a powerful tool to characterize the heterogeneous changes associated with neurodegenerative diseases.

Disclosures: X. Sun: None. **L. Wu:** A. Employment/Salary (full or part-time):; Nanostring Technologies Inc, Bruker. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nanostring Technologies Inc, Bruker. **A. Heck:** A. Employment/Salary (full or part-time):; Nanostring Technologies Inc, Bruker. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nanostring Technologies Inc, Bruker. **K. Young:** A. Employment/Salary (full or part-time):; Nanostring Technologies Inc, Bruker. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nanostring Technologies Inc, Bruker. **T. Orr:** None. **M. Orr:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.03/B132

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

Title: Identification of lipids bound to amyloidogenic proteins

Authors: *A. PAQUOLA[1], E. ACQUARONE[1], F. ZANDKARIMI[2], O. ARANCIO[1];
[1]Columbia Univ., NEW YORK, NY; [2]Columbia Univ., Dept. of Chem., NEW YORK, NY

Abstract: The context in which the oligomerization of amyloidogenic proteins starts *in vivo* is still not well understood. One of the amyloidogenic proteins that has been more extensively studied is Tau. Tau is a microtubule-associated protein that has been found in neurofibrillary tangles in the brain of patients with Alzheimer's disease (AD). Tau has been reported to interact with cellular membranes and lipid membranes have been shown to enhance its aggregation *in vitro*. Interestingly, it has been shown that the affinity of Tau for lipids is highly dependent on electrostatic interactions and phospholipid head group composition. Despite these studies, it is still not known what lipids interact with Tau *in vivo*. It is our hypothesis that specific lipid species could promote Tau aggregation in oligomers. The first step to test this hypothesis is to determine which specific lipids are bound to Tau in physiological conditions. We optimized a technique to isolate the lipids interacting with Tau from wild-type mice and observed that murine Tau in physiological conditions interacts with a wide variety of phospholipids, including phosphatidylinositol and phosphatidylglycerol. These results are consistent with the previous *in vitro* studies. We are now isolating the lipids bound to human Tau from control and AD patients. To unveil the role of lipids in AD pathology, we want next to understand if oligomeric and monomeric Tau bind distinct lipid species. Our goal is then to apply this approach systematically to other amyloidogenic proteins, including beta-amyloid and alpha-synuclein.

Disclosures: A. Paquola: None. **E. Acquarone:** None. **F. Zandkarimi:** None. **O. Arancio:** Other; Founding Member of Neurokine Therapeutics, Advisory Board of Appia Pharmaceutical..

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.04/B133

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

Support: NIH R00AG068271
HudsonAlpha Foundation

Title: Identification of Cis-Regulatory Elements for MAPT using Massively Parallel Reporter Assays

Authors: *R. M. HAUSER[1], B. MOYERS[1], S. LAUZON[2], J. N. BRAZELL[1], E. BARINAGA[1], J. COCHRAN[1];
[1]HudsonAlpha Inst. for Biotech., Huntsville, AL; [2]The Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Intracellular tau neurofibrillary tangles are pathological hallmarks of several neurodegenerative diseases falling under the umbrella of tauopathies. In addition, genetic variation at the 17q21.31 region spanning MAPT has been associated with increased risk for several neurodegenerative diseases. However, functional genomics knowledge for this locus is limited, including how MAPT (tau) is regulated. Elucidating the molecular mechanisms of regulation for MAPT and other genes in this region will provide important insights. Through the identification and characterization of cis-regulatory elements (CREs) in non-coding regions of the genome at this locus, we can also further understand potential disease risk in individuals with genetic variants in regulatory regions.To functionally assess the transcriptional activity of the locus, 24 Bacterial Artificial Chromosomes (BACs) containing human DNA spanning 3 Mb around the MAPT locus were sheared to a size of ~250 bp. In addition to the sheared BACs, we synthesized a pool of 17,988 oligos tiling the MAPT locus to use as test elements for Massively Parallel Reporter Assays (MPRAs) in human neurons. The test elements were barcoded, ligated into a lentiMPRA vector, packaged into lentivirus, and transduced into excitatory neurons differentiated from the KOLF2.1J-NGN2 iPSC line. DNA and RNA were collected from both neurons and the lentivirus producer cells (HEK293FTs), then each sheared BAC and oligo sequence was associated with a barcode through NGS sequencing. The occurrences of each barcode's DNA and RNA were counted, and counts were compared using MPRAflow and MPRAnalyze as a proxy for test element regulatory activity. Several regulatory regions identified in the MPRAs were also nominated as putative CREs for MAPT using both chromatin conformation assays indicating proximity to the MAPT promoter and overlap of single nucleus multiomics data (snRNA- + snATAC-seq), providing strong evidence for their roles in MAPT regulation. Additionally, this evidence supports their testing using CRISPRi to determine if these nominated regions are necessary for MAPT expression.Overall, we successfully used both sheared BACs and synthesized oligos as input material for MPRAs in iPSC-derived neurons investigating the regulatory potential of a region of more than three million base pairs around MAPT. Through this, we identified several cell type-specific CREs with positive regulatory activity in both neurons and HEK293T cells. Future directions include exploring the role of genetic variation at these CREs to determine if there is an effect on regulatory ability.

Disclosures: R.M. Hauser: None. **B. Moyers:** None. **S. Lauzon:** None. **J.N. Brazell:** None. **E. Barinaga:** None. **J. Cochran:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.05/B134

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

Support: R01AG057914
R01AG054180
A2021010F

Title: Using complex genetics in mice to unlock the secrets of resilience to dementia

Authors: *S. MOORE[1], N. HADAD[2], V. A. JANVE[3], S. CANCHI[4], V. M. PHILIP[5], T. J. HOHMAN[6], V. MENON[7], C. C. KACZOROWSKI[8];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Neurosci., TGen, Phoenix, AZ; [3]Biomed. Engin., Vanderbilt Univ., Nashville, TN; [4]Neurosciences, UCSD Sch. Med., La Jolla, CA; [5]Computat. Sci., The Jackson Lab., Bar Harbor, ME; [6]Vanderbilt Memory & Alzheimer's Ctr., Nashville, TN; [7]Neurol., Columbia Univ., New York, NY; [8]Neurol., The Univ. of Michigan, Ann Arbor, MI

Abstract: Aims: Cognitive resilience to Alzheimer's disease (AD) is a phenomenon whereby an individual presents with normal cognitive function despite harboring a familial Alzheimer's disease (FAD) mutation and has corresponding brain neuropathology. Determination of the underlying mechanisms of cognitive resilience to AD will likely offer novel disease modifying therapeutics for individuals at-risk for AD. **Methods:** We used the contextual fear memory paradigm to assess short-term memory function in the AD-BXD mouse reference panel, which incorporates the 5xFAD human mutations on a genetically diverse background that better mimics human AD. The degree resilience or susceptibility was based on the age-related change in cognitive function relative to that of the entire AD-BXD population; strains showing no or lower than average decline were considered resilient, while those showing more decline were considered susceptible. To determine transcriptional changes associated with resilience, we profiled the hippocampal transcriptome at the single cell level in top resilient and susceptible strains. **Results:** We show that cognitive resilience in 5xFAD mice is characterized by a transcriptional signature that aligns with that of non-transgenic littermates in excitatory neurons of CA1, dentate gyrus and intratelencephalic neurons in layer 3 and 6 of the entorhinal cortex. We found that the transcriptional profile of resilient strains is enriched for regulation of transmembrane transport in presymptomatic stages that included a notable upregulation of Reln and Ntng2, whereas translation at the CA1 synapse corresponded to an upregulation of ribosomal genes in neurons from resilient AD mutation carrier mice. **Conclusions:** Our findings suggest that resilience is conferred in memory-relevant regions through unique transcriptional changes in a cell-specific manner and provide a foundation for mechanistic studies required for resilience-based drug development.

Disclosures: S. Moore: None. **N. Hadad:** None. **V.A. Janve:** None. **S. Canchi:** None. **V.M. Philip:** None. **T.J. Hohman:** None. **V. Menon:** None. **C.C. Kaczorowski:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.06/B135

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

Title: Transcriptomic identification and in situ validation of an early-affected, tau-vulnerable neuronal subtype in the progression of human Alzheimer's disease

Authors: *S. CHANCELLOR[1], G. LIN[2], T. KWON[4,3], M. WOODBURY[3], A. WACHTER[5], N. ROMANUL[3], K. YANAMANDRA[3], R. E. BENNETT[6], Y. GRINBERG[3], S. DAS[6], A. SERRANO-POZO[6], B. HYMAN[6], X. LANGLOIS[3];
[1]AbbVie Inc., Cambridge, MA; [2]AbbVie, Inc., Singapore, Singapore; [3]AbbVie, Inc., Cambridge, MA; [4]Res., AstraZeneca, New Haven, CT; [5]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany; [6]Neurol., Harvard Med. School, Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Tau pathology is considered a primary driver of neurodegeneration in Alzheimer's disease (AD), but its molecular mechanisms are still unclear. Several previous single-nucleus RNA sequencing (snRNA-seq) studies have identified neuronal subtypes in human AD samples that appear vulnerable to AD pathology through associations with global and local measures of neuropathological burden (Mathys et al., 2023, Gazestani et al., 2023). In the current study, we sought to identify region-specific neuronal subpopulations vulnerable to tau pathology through snRNA-seq and quantitative neuropathological analyses in a sample of brain donors selected to represent the normal aging-severe AD continuum (Braak 0 to VI, n = 30) and multiple brain regions selected to represent the AD-vulnerable brain network (entorhinal cortex, inferior temporal gyrus, prefrontal cortex, and primary/secondary visual cortices). For each fresh-frozen brain specimen, we collected adjacent tissue sections for snRNA-seq, phospho-tau ELISA, HEK cell-based tau seeding assays, and imaging-based quantitative neuropathological studies. We investigated whether the relative number of the detected neuronal subtypes changes with tau pathology by testing for an association between phospho-tau levels and neuronal subtype abundance. We subsequently identified a subcluster of excitatory neurons in the inferior temporal gyrus and prefrontal cortex with vulnerability to increasing tau pathology. Multiplexed immunohistochemistry and in situ hybridization validated the presence of this tau-vulnerable neuronal population in adjacent sections to those used for snRNA-seq and revealed a propensity within this population for bearing tau aggregates compared to other neurons, even in early disease stages. The discovery of the transcriptional profile of this cellular subtype can be leveraged to further understand the molecular underpinnings of susceptibility to neuronal tau pathology.

Disclosures: S. Chancellor: A. Employment/Salary (full or part-time):; AbbVie, Inc. **G. lin:** A. Employment/Salary (full or part-time):; AbbVie, Inc. **T. Kwon:** A. Employment/Salary (full or part-time):; AbbVie, Inc. **M. Woodbury:** A. Employment/Salary (full or part-time):; AbbVie, Inc. **A. Wachter:** A. Employment/Salary (full or part-time):; AbbVie, Inc. **N. Romanul:** A. Employment/Salary (full or part-time):; AbbVie, Inc. **K. Yanamandra:** A. Employment/Salary (full or part-time):; AbbVie, Inc. **R.E. Bennett:** A. Employment/Salary (full or part-time):; Massachusetts General Hospital. **Y. Grinberg:** A. Employment/Salary (full or part-time):; AbbVie, Inc. **S. Das:** A. Employment/Salary (full or part-time):; Massachusetts General

Hospital. **A. Serrano-Pozo:** A. Employment/Salary (full or part-time):; Massachusetts General Hospital. **B. Hyman:** A. Employment/Salary (full or part-time):; Massachusetts General Hospital. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; AbbVie, Inc., AvroBio, Axon, Biogen, BMS Cell Signaling, Genentech, Ionis, Novartis, Seer, Takeda, US Dept. of Justice, Vigil, Voyager, F Prime, NIH, Tau Consortium, JPB Foundation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Novartis, Dewpoint. F. Consulting Fees (e.g., advisory boards); Dewpoint. **X. Langlois:** A. Employment/Salary (full or part-time):; AbbVie, Inc..

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.07/B136

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

Title: Insights into the mechanism of action of semaglutide in Alzheimer's disease as assessed by shotgun proteomics

Authors: D. KATSAVELIS[1,2], *M. G. C. VAN DER HART[2,3], H. A. KOOIJKER[4], J. ROESER[4], H. P. PERMENTIER[1], **T. I. F. H. CREMERS**[4,2,3];
[1]IMSC, Univ. of Groningen, Groningen, Netherlands; [2]Quantall BV, Groningen, Netherlands; [3]Imsc, University of Groningen, Groningen, Netherlands; [4]Quantall LLC, Mountain View, CA

Abstract: Semaglutide is a peptide similar to glucagon-like-protein 1 and is effective in the treatment of obesity and diabetes type 2. Recently, semaglutide has also been studied for its efficacy in Alzheimer's disease. Although preclinical and clinical data seems to be positive, little is known about its central mechanism of action in the brain and Alzheimer's disease.
Shotgun proteomics uses high resolution mass spectrometry in combination with liquid chromatography to measure thousands of proteins within a single sample. This method allows for an unbiased study of biomarkers and can shed light on mechanistic cascades induced by drug administration or the development of certain pathologies.
In this study we investigated the effect of semaglutide administration on protein expression in the brain. For this purpose, we used shotgun proteomics to study changes in protein expression as a result of semaglutide administration.
Semaglutide or vehicle was subcutaneously administered in mice. Three hours after administration, brain tissue was harvested and snap frozen until further analysis. Upon sample preparation and protein digestion, samples were analyzed using a nanoflow LC-system coupled to an Orbitrap Exploris 480 high resolution mass spectrometer, acquisition was done in DIA mode and processed using specialized proteomics software for protein identification and quantification.
Depending on sample preparation methods and software settings, up to 2000 proteins could be

identified. Deviations between and within run quality control samples, indicated large variations between the sample preparation methods used. Extended data analysis beyond statistical analysis and fold change, revealed the importance of monitoring a wide parameter range while performing unlabeled proteomics.
Semaglutide administration induced differentially expressed proteins within the brain. These proteins could be correlated to concurrent genes and to underlying mechanistic pathways like cognition, metabolism, neurogenesis and apoptosis.
Using stringent criteria for rating biomarkers in shotgun proteomics, multiple mechanistic events are identified that might be relevant to the therapeutic effects of semaglutide in Alzheimer's disease.

Disclosures: D. Katsavelis: None. **M.G.C. van der Hart:** None. **H.A. Kooijker:** None. **J. Roeser:** None. **H.P. Permentier:** None. **T.I.F.H. Cremers:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.08/B137

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

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Title: Mapping the spatial proteome signature of hippocampal subfields in early Alzheimer's disease: changes in memory and synaptic plasticity-related proteins with sexual dimorphism

Authors: *A. CONTRERAS, R. JIMÉNEZ-HERRERA, S. DJEBARI, J. D. NAVARRO-LOPEZ, L. JIMENEZ-DIAZ;
Neurophysiol. and Behaviour Lab., Univ. of Castilla-La Mancha, Ciudad Real, Spain

Abstract: An initial neuropathological hallmark of Alzheimer's disease (AD) is the hippocampal dysfunction caused by amyloid-β (Aβ) peptides accumulation. Soluble oligomeric forms of Aβ (oAβ) shift synaptic plasticity induction threshold leading to memory deficits in male and female mice in early amyloidosis' models. Some protein changes underlying those deficits have been previously studied, but the spatial distribution within the hippocampus, as well as the potential sex differences, remain unknown. Since each hippocampal region (dorsal *vs*. ventral) and subfield (CA1, CA2, CA3 and DG) has clearly distinct functionality and connectivity, we postulated that some protein changes may be unique to each and might also be sexdependent. Thus, an innovative spatial proteomics study was performed to map whole hippocampal proteome distribution using matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry, which allows protein detection with spatial resolution directly on tissue sections.

Brains from sixteen adult male and female mice intracerebroventricularly injected with oA$\beta_{1\text{-}42}$ or vehicle were used. MALDI imaging was performed using a RapifleXTM MALDI TissuetyperTM TOF/TOF mass spectrometer followed by protein identification by traditional tandem mass spectrometry (MS/MS) directly on the tissue. To precisely delineate each hippocampal region and subfield, a Nissl staining was performed on succeeding tissue sections. Overall, our results showed alterations in both male and female mice after a single *icv.* oA$\beta_{1\text{-}42}$ injection in the expression of several key proteins related to memory formation and the underlying synaptic plasticity processes. Furthermore, many of the altered proteins modulate glycogen synthase kinase-3β (GSK-3β), a protein widely involved in the regulation of synaptic plasticity induction threshold. In fact, hippocampal GSK-3β was found overactivated, suggesting a facilitated long-term depression (LTD) instead of long-term potentiation (LTP) in AD. To the best of our knowledge, our work is the first that provides a mapping of the spatial distribution of the hippocampal subfields' proteome in both male and female mice, which might provide a specific signature of biomarkers of AD's early stages. Furthermore, our results provide new valuable potential biomarkers for early diagnosis and therapeutic targets.

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Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

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Program #/Poster #: PSTR012.09/B138

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

Support: JPND HEROES project
Sello Excelencia ISCIII-Health Grant IHMC22/00026

Title: Common pathogenic mechanisms in the hippocampus of Parkinson's disease, Alzheimer's disease and Down syndrome

Authors: *R. A. J. CRANS[1], K. BASCÓN CARDOZO[1], M. FRUCTUOSO[2], D. VAN DAM[3], P. DE DEYN[4], M.-C. POTIER[2], M. DIERSSEN[1];
[1]Ctr. for Genomic Regulation, Barcelona, Spain; [2]CNRS INSERM SORBONNE Univ., CNRS INSERM UPMC, Paris, France; [3]Dept. of Neurol. and Alzheimer Res. Ctr., Univ. of Groningen, Groningen, Netherlands; [4]Univ. of Antwerp, Antwerp (Wilrijk), Belgium

Abstract: Over the age of 40, most individuals with Down syndrome (DS, or trisomy 21) develop dementia with senile plaques and neurofibrillary tangles, as observed in Alzheimer's disease (AD). Around 15% of patients with Parkinson's disease (PD) progress to a stage with severe dementia. On the other hand, Lewy bodies, the main neuropathological hallmark PD, are often found in AD apart from plaques and tangles. These data indicate that these pathologies might share key molecular processes. The degeneration of the locus coeruleus (LC) has recently

been postulated as the common pathogenic mechanism between DS, AD and PD. The noradrenergic neurons descending from the LC mediate memory, attention and arousal. Consequently, LC neuronal loss affects the function of target areas, including the hippocampus. The goal of this study was to uncover the underlying biomolecular processes through the identification of commonly up/downregulated genes and molecular pathways within the LC and one of its target areas (*i.e.*, hippocampus).
To this aim, total RNA (*i.e.*, non-mRNA enriched) was isolated from LC and hippocampal tissues of 25 and 28 individuals, respectively, including healthy controls, DS, PD and AD cases (n = 5/10 per group). Sequencing libraries were prepared, paired-end bulk RNA-sequencing (RNA-seq) was performed and reads of the FastQ files were mapped with STAR. The differential expressed genes (DEGs) were identified for each pathology (*i.e.*, DS, AD and PD) against healthy controls with voom + limma using R version, controlling for Sex, RIN and RNAAge. Multiple testing was carried out by FDR-correction with a cutoff for DEGs of adjusted p-value < 0.1 & logFC < 0.5 & logFC > 0.5.
Hierarchical clustering and principal component analysis clearly separate the samples of the two brain regions. As expected, the individuals with DS had mainly upregulated genes of chromosome 21, while AD and PD patients showed up- and downregulation of gene expression across all the chromosomes. A total of 7 commonly upregulated genes between the pathologies were discovered in the LC, whereas 72 upregulated genes and 28 downregulated genes were shared among the pathologies in the hippocampus.
Overall, our data suggest common molecular mechanisms between DS, AD and PD postmortem human hippocampal tissues, a brain region that is affected by the early degeneration of noradrenergic projecting neurons from the LC.

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Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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

Support: NIH R01 AG081426
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NIH T32 AG029796-16

Title: Apoe genotype modulates mitochondrial function and multi-omic profiles in humanized mouse models

Authors: *A. CHANG[1], B. AN[2], W. QU[3], M. GLITTENBERG[4], D. LI[5], L. LI[6];
[1]Grad. Program in Neurosci., Univ. of Minnesota, Minneapolis, MN; [2]Dept. of Lab. Med. and Pathology, Univ. of Minnesota, Twin Cities, Minneapolis, MN; [3]Neurosci., Weill Cornell Med.,

New York, NY; [4]Univ. of Wisconsin-Madison, Madison, WI; [5]Dept. of Lab. Med. and Pathology, Univ. of Minnesota, Minneapolis, MN; [6]Exptl. and Clin. Pharmacol., Univ. of Minnesota, Minneapolis, MN

Abstract: APOE4 is the primary genetic risk factor for late-onset Alzheimer's disease (AD), the most prevalent cause of dementia worldwide. APOE functions as a key lipid transporter in the brain, with additional functions in neuronal growth, synaptogenesis, immunomodulation, and proteostasis, including Aβ clearance/degradation and tau aggregation/toxicity. Previous investigations in our lab have revealed that compared to APOE3, APOE4 expression in mouse cortex is linked to lipid and metabolite alterations associated with mitochondrial function. These findings parallel observed mitochondrial dysfunction in AD, characterized by reduced glucose and oxygen utilization, impaired respiratory chain function, and mitochondrial DNA abnormalities, all correlated with extracellular Aβ and intracellular tau accumulation. The goal of this study is to investigate mitochondrial multi-omic alterations in the brain of humanized APOE3/3 (E3/3) and APOE4/4 (E4/4) knock-in mice. We performed RNA-sequencing of cortical tissue in 13-month-old E3/3 and E4/4 mice and utilized the MitoCarta 3.0 database to identify differentially expressed mitochondrial genes (mito-DEGs). E4/4 mice exhibited a general upregulation of mitochondrial oxidative phosphorylation (OXPHOS) subunits alongside downregulation of genes related to mitochondrial ribosomes. Pathway enrichment analysis highlighted upregulated mitochondrial pathways in E4/4 mice, including amino acid metabolism and OXPHOS-related pathways, suggesting potential compensatory mechanisms for mitochondrial impairment. Ongoing lipidomics and metabolomics studies aim to uncover changes in the lipidome/metabolome within distinct brain mitochondrial pools: non-synaptic mitochondria from neuronal and glial cells, and synaptic mitochondria within neuronal synapses. Initial results will be presented along with analyses correlating mitochondrial lipidomic profiles with transcriptomic changes to elucidate cellular and molecular pathways underlying the impact of APOE genotype on AD.

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Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.11/B140

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

Title: Loss of FTD/ALS-Associated RNA Binding Proteins Alter Axonal mRNA Transport and Translation

Authors: *R. DARGAN;
NIH, bethesda, MD

Abstract: RNA binding proteins (RBPs) are essential to neuronal function due to their involvement in transport of mRNA transcripts to distal processes of the cell for local translation. Interestingly, in FTD/ALS (Frontotemporal dementia/amyotrophic lateral sclerosis), there are mutations in RBPs that disrupt these processes leading to mislocalization, aggregation, and abnormal alternative splicing. These mutations can have a loss of function (LOF) effect such as inability to shuttle transcripts or a gain of function (GOF) impact like aggregation. Since it is unclear the role of these disease associated mutations in the development of FTD/ALS, we aimed to understand the effects of LOF of RBPs (TDP-43, hnRNPA1 and FUS) on transport and translation in iPSC-derived neurons. In the RBP knockdowns, FISH (fluorescent in situ hybridization) and RNA-sequencing reveal increased localization of mRNA transcripts in the neurites, however proteomics identifies differential protein expression, suggesting an issue with local translation. Interestingly, there was an increase in proteins of the same family or those that have a similar function to our target RBPs, indicating a compensation mechanism that could help our understanding of the role of LOF RBPs. Our current analysis on wild type neurons reveals that proteins translated in our neurites are associated with Parkinson's, ALS, Alzheimer's disease and other pathways of neurodegeneration. We are currently focusing on identifying the nascent proteins being translated in the peripheries of KD neurons through local translation assays: QuanCAT (quantitative non canonical amino acid tagging) and SILAC (stable isotope labeling using amino acids in cell culture). Our results show that the neuritic transcriptome does not equal the neuritic proteome and that a potential protein compensatory mechanism partially mitigates RBP LOF. This discovery will aid in understanding the role of RBPs and their associated mutations in neurodegeneration.

Disclosures: R. Dargan: None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.12/B141

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

Support: NIH grant AG064244
NIH grant AG070075

Title: Comprehensive aberrations of the proteasome complex in Alzheimer's Disease

Authors: S. JIANG, ***M. SRIKANTH**, S. YAVARI, N. MYEKU;
Columbia Univ., New York, NY

Abstract: The ubiquitin-proteasome system (UPS) is the primary protein degrading mechanism in eukaryotes and is essential for cellular homeostasis. Dysregulation of the UPS has been linked to neurodegeneration through two key hallmarks: pathogenic protein aggregation and aberrant proteostasis. This indicates a central role of the UPS in AD pathogenesis. However, the

molecular changes underlying proteasome dysfunction in AD are poorly understood. We hypothesized that proteasomes in the AD brain are affected across various levels, encompassing functional attributes, proteomics profiles, and transcriptional regulation. We observed that proteasomes from AD brain tissue showed a decrease in substrate degradation rate in kinetics assays compared to age-matched controls, corroborated by native in-gel activity assays. Proteomics analysis revealed diminished levels of proteasome subunits comprising the 20S and 19S particles and a considerable proteasomal burden of phosphorylated tau in AD brains. Interrogation of bulk and snRNA-seq datasets uncovered a down-regulation in the expression of constitutive proteasomes in brain tissue from early Braak stages, primarily in neurons. Subsequent analysis of RNA-seq datasets from iPSC-derived neurons and cerebral organoids showed a down-regulation of proteasome genes in A-beta and tauopathy models compared to isogenic controls. To investigate the transcriptional down-regulation of proteasome complexes in AD, we turned to NFE2L1 (Nrf1), a master transcription factor that regulates proteasome subunit genes expression and mediates the proteasome bounce-back response when proteasome activity is impaired. Leveraging DS1 (non-tau aggregating) and DS9 (tau aggregate-forming) clonal cell lines, we found that DS9 cells showed significantly increased levels of nuclear NFE2L1 compared to DS1 cells. This indicated the activation of the bounce-back response. Notably, this bounce-back response appears to be impaired in human AD brain tissue, which we envisage leads to the down-regulation of proteasome genes demonstrated by our omics and functional approaches. Our study shows that proteasome activity is reduced in AD due to neuronal transcriptional down-regulation of proteasome genes early in the disease pathogenesis. In turn, the accumulation of tau aggregates compromises proteasome functions, engaging in a negative feedback loop of proteotoxicity. Moreover, we show that the Nrf1 signaling cascade is impaired in AD, which could explain why AD brain tissue exhibits low levels of proteasome complexes.

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Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

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

Support: NIH grant 1U24NS133077-01
NIA grant U19AG060909

Title: Annotation Comparison Explorer (ACE): connecting brain cell types across studies of health and Alzheimer's Disease

Authors: *J. A. MILLER[1,2], K. J. TRAVAGLINI[3], T. LUQUEZ[4], R. E. HOSTETLER[3], A. OSTER[5], B. TASIC[5], V. MENON[6];
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]Human Cell Types, Allen Institute for Brain Science, Seattle, WA; [3]Human Cell Types, Allen Inst. for Brain Sci., Seattle, WA; [4]Neurology/Pathology,

Columbia Univ., New York, NY; [5]Cell and Circuit Genet., Allen Inst. for Brain Sci., Seattle, WA; [6]Neurol., Columbia Univ., New York, NY

Abstract: Single-cell multiomic technologies have allowed unprecedented access to gene profiles of individual cells across species and organ systems, including >1000 papers focused on brain cell types alone. The Allen Institute has created foundational atlases characterizing mammalian brain cell types in the adult mouse brain and the neocortex of aged humans with and without Alzheimer's disease (AD). With so many public cell type classifications (or 'taxonomies') available and many groups choosing to define their own, linking cell types and associated knowledge between studies remains a major challenge. Here, we introduce Annotation Comparison Explorer (ACE), an R shiny and web-based application for comparing cell type assignments and other cell-based annotations (e.g., donor demographics, anatomic locations, batch variables, and quality control metrics). ACE allows filtering of cells and includes an interactive set of tools for comparing two or more taxonomy annotations alongside collected knowledge (e.g., increased abundance in disease conditions, cell type aliases, or other information about a specific cell type). We present three use cases for ACE. First, we have collated and reprocessed through a common pipeline data from ten published human AD studies and have assigned cell type labels from the Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD) taxonomy to cells from each study. This allowed us to compare brain taxonomies across otherwise incomparable studies and identify congruent cell type abundance changes in AD, including a decrease in abundance of some (but not all) somatostatin interneurons. Second, we demonstrate how a user can map their data to this reference and compare their cell type assignments with SEA-AD cell types directly. Finally, ACE includes translation tables between different cell type taxonomies publicly accessible on Allen Brain Map, including in human middle temporal gyrus and mouse primary visual cortex. ACE can be freely and publicly accessed at github.com/AllenInstitute/ACE.

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Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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

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Title: Use ofspatial transcriptomics and proteomics to understand Alzheimer's Disease

Authors: C.-T. LEE[1], L. WU[2], A. HECK[2], L. ZHANG[1], E. LAI[1], B. DOMINGUEZ[1], K. YOUNG[2], A. ROSENBLOOM[2], E. BOOKER[1], X. WANG[1], C. WILLIAMS[2], A. WILLIAMS[1], P. KOSURI[1], D. A. BENNETT[3], J. M. BEECHEM[4], ***K.-F. LEE**[1];
[1]Salk Inst., La Jolla, CA; [2]NanoString Technologies, Seattle, WA; [3]Rush Alzheimer's Dis. Ctr., Rush Univ. Med. Ctr., Chicago, IL; [4]Nanostring Technologies, Piedmont, CA

Abstract: Selective vulnerability of both neurons and non-neuronal cells and/or synaptic sites is at the heart of the logic for understanding the initiation and progression of AD. Several lines of evidence suggest that AD is initiated in sub-cortical regions. Among the regions affected early in the disease are the locus coeruleus, entorhinal cortex, hippocampus and prefrontal cortex. Importantly, these four brain regions project to each other and to multiple targets to form specific connection hubs that sequentially or co-currently degenerate. Thus, establishing atlases for both neurons and non-neuronal cells selectively susceptible to proteinopathies (e.g., Aβ plaques and Tau tangles) is an important step to uncover the underlying disease mechanisms. Spatial transcriptomics and proteomics have emerged as a powerful tool in the multi-scale modeling approach to unlock the AD logic. Here we employ the CosMx™ Spatial Molecular Imager (SMI) platform for high plex detection of 6,000 RNAs and 72 proteins in the same FFPE human brain sections in spatial context. This multi-omics assay involves first detecting proteins with oligonucleotide barcode-conjugated antibodies and then exposing sections to protease digestion and detecting RNAs with barcoded RNA probes. Detection of each analyte relies on barcode readout on the SMI instrument via several rounds of reporter binding and fluorescence imaging utilizing universal SMI readout reagents that work for both RNA and protein assays. With the SMI multi-omics approach, it is ultimately possible to use high plex protein data from a large area of tissue to identify smaller regions of interest on the same slide, which offers a more comprehensive view of the neurobiological picture in healthy vs. diseased brain sections. Whereas the protein panel focuses on neural cell typing and neurodegenerative disease pathology (including phospho-tau variants and Aβ 40/42), the ultra-high plex RNA panel includes >4,900 neuroscience-related genes, covering >80 pathways and enabling robust neuronal and glial cell typing as well as exploration of key ligand-receptor interactions. For example, this approach would allow us to determine the spatial relationship between A42/40 ratios of each plaque and distance of impaired cell types and magnitude of de-regulated genes or proteins. Thus, through the high plex multi-omic approach, we demonstrate the use of SMI spatial molecular imaging to create a spatial atlas of vulnerable brain cell types, define neighborhoods, and probe numerous pathways and cellular phenotypes.

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Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.15/C2

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

Support: NIH Grant 5R44AG065051-02

Title: Identification of novel biomarkers for Alzheimer's Disease and related dementias using unbiased plasma proteomics

Authors: B. L. LACAR[1], **E. YANG**[1], *S.-Y. CHEN[1], B. HYMAN[2], S. E. ARNOLD[3], S. DAS[3], P. KIVISÄKK[3], S. BATZOGLOU[1];
[1]Seer Inc., Redwood City, CA; [2]Neurol., Massachusetts Gen. Hosp., madison, NH;
[3]Massachusetts Gen. Hosp., Boston, MA

Abstract: Early detection and intervention provide the best chance for prevention of Alzheimer's disease (AD) and related dementias (ADRD). Some blood-based biomarkers, especially pTau, have emerged with good-excellent discrimination of patients with AD in particular (as determined by amyloid PET or cerebrospinal fluid amyloid and tau biomarkers). However, ADRDs are complicated disorders with multiple pathophysiological drivers determining progression and clinical features. Identification of a broader set of blood-based biomarkers is essential to characterize these multiple drivers for better prognosis, clinical management, and targeted treatments. In this study, we aim to leverage unbiased mass spectroscopy proteomics to identify novel, blood-based biomarkers associated with progression of cognitive decline. 1790 plasma samples from 1006 patients were collected over 12 years as part of the Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort Study. Patient metadata includes demographics and clinical dementia rating (CDR) scores taken concurrently. Proteograph Product Suite (Seer Inc.) and liquid-chromatography mass-spectrometry analysis was used to process the plasma samples in this cohort and generate proteomics data. Subsequently, we built Cox proportional hazards (CPH) models to evaluate the association of protein group levels with time to progression of the global Clinical Dementia Rating score. Data-independent acquisition (DIA) mass spectrometry results yielded 36,259 peptides and 4,007 protein groups. In CPH models, we find multiple protein groups significantly associated with either accelerated or delayed cognitive decline. We demonstrate the Proteograph workflow's ability to perform unbiased, deep, and rapid interrogation of the plasma proteome, enabling large-scale studies, and revealing novel insights with clinically relevant potential. Future work will focus on understanding the similarities and differences in the pathophysiological pathways associated among ADRD, as well as heterogeneities among AD stage and subtypes.

Disclosures: B.L. Lacar: A. Employment/Salary (full or part-time):; Seer Inc. **E. Yang:** A. Employment/Salary (full or part-time):; Seer Inc. **S. Chen:** A. Employment/Salary (full or part-

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Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.16/C3

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

Support: AG072599
AG074004
AG077103
AG014449
AG085572
AG061869

Title: Overview of dysfunctional Protein-Protein Interactome (dfPPI): a platform for systems-level protein-protein interaction (PPI) defects in neurodegenerative disorders

Authors: *S. D. GINSBERG[1,2,3,4], S. CHAKRABARTY[5], S. WANG[5], T. ROYCHOWDHURY[5], S. BAY[5], A. RODINA[5], M. J. ALLDRED[1,2], A. LABUZA[1,2], A. STANISAVLJEVIC[1], H. ERDJUMENT-BROMAGE[6], T. A. NEUBERT[6], G. CHIOSIS[5,7]; [1]Ctr. for Dementia Res., Nathan Kline Inst., Orangeburg, NY; [2]Psychiatry, New York University Grossman School of Medicine, New York, NY; [3]Neuroscience & Physiology, New York University Grossman School of Medicine, New York, NY; [4]NYU Neuroscience Institute, New York University Grossman School of Medicine, New York, NY; [5]Chem. Biol. Program, Mem. Sloan Kettering Cancer Ctr., New York, NY; [6]Cell Biol., New York Univ. Grossman Sch. of Med., New York, NY; [7]Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract: Background: Protein-protein interactions (PPIs) play a crucial role in cellular function and disease manifestation, with dysfunctions in PPI networks providing a direct link between stressors and phenotypes. dysfunctional Protein-Protein Interactome (dfPPI), formerly known as epichaperomics, is a newly developed chemoproteomic method. dfPPI is capable of detecting dynamic changes at the systems level in PPI networks under stressor-induced cellular perturbations within disease states, including neurodegenerative disorders such as the Alzheimer's disease (AD) spectrum ranging from no cognitive impairment (NCI) to mild cognitive impairment (MCI), and AD. In neurodegenerative disorders, dfPPI uncovers critical dysfunctions in cellular processes and stressor-specific vulnerabilities. The dfPPI platform is a potent tool for dissecting disease systems biology by directly informing on dysfunctions in PPI networks and holds promise for advancing disease identification and therapeutics during AD onset and progression.
Hypothesis: Supported by foundational discoveries in disease biology, dfPPI offers a unique lens through which to understand how stressor-induced perturbations in interactome networks

manifest through the formation of epichaperomes. By capturing these pathological scaffolds and their impacted interactors, dfPPI provides translational and potentially transformative insights into the context-dependent rewiring of PPIs and their downstream functional consequences within native biological systems, including revealing pathological changes across the AD spectrum. These include PPIs underlying synaptic dysfunction, bioenergetics, and oxidative phosphorylation defects.
Conclusions: An advantage of dfPPI lies is its ability to investigate PPI network dysfunctions in disease. This direct exploration sheds light on stressor-to-phenotype relationships, offering context-dependent insights into dysfunction, including AD. Because epichaperomics is a 'sensor' to stressor induced dysfunctions into molecular mechanisms it is also an excellent tool to gain unbiased system levels insights into how differential vulnerability to stressors associated with individual patient's disease (e.g., genetic, clinical, environmental, proteotoxic, among others) for precision medicine treatment approaches towards neurodegenerative disorders.

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Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.17/C4

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

Title: Characterizing the Genetic Expression Profile of an Alzheimer's Disease risk gene TREM2 Variant in a Co-Culture Model of Organoids and Microglia

Authors: *A. KAMZINA, K. E. LEINENWEBER, A. ALDABERGENOVA, M. HUENTELMAN;
Neurogenomics, TGen, Phoenix, AZ

Abstract: Microglia cells play a primary role in maintaining homeostasis in human brain by clearing debris and waste through phagocytosis. In Alzheimer's disease (AD), however, microglia actions are a double-edged sword which can lead to deleterious outcomes contributing to neuronal damage and neuroinflammation, mainly in the disease's later stages. This harmful transition is partly influenced by the microglia receptor, Triggering Receptor Expressed on Myeloid Cells 2 (TREM2). Genetic variation in TREM2, such as the low-frequency R47H change, is associated with an increased risk of AD. In this work, we utilize CRISPR-modified iPSC-derived forebrain organoids and microglia to investigate the inflammatory mechanisms and neurodegeneration linked to this genetic variant. We grew these organoids for up to day 150 and co-cultured with microglia. We performed both bulk RNA and single-cell RNA sequencing to analyze the transcriptomic profiles using DESeq and Seurat in R. We observed increased

phosphoTau(Thr-231)/total Tau protein expression in older organoids, confirmed by immunoassay (MSD) and immunostaining, which also verified successful microglia integration. While data collection and analysis for these experiments are still in progress, preliminary results suggest that co-culturing microglia with brain organoids harboring an AD risk-associated variant facilitates the identification of genetic transcriptional shifts and molecular pathway activities. Collectively, these findings provide insights into the molecular dynamics of the R47H TREM2 variant in a controlled, physiologically relevant microenvironment. This approach opens new avenues for applying genetic variant-specific research to enhance our understanding of AD and develop precision medicine strategies and better therapeutic options.

Disclosures: A. Kamzina: None. **K.E. Leinenweber:** None. **A. Aldabergenova:** None. **M. Huentelman:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.18/C5

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

Support: NIH P30 AG066509
Nancy and Buster Alvord Endowment

Title: Disentangling the relationship between pathology and cell-specific vulnerability using large format highly multiplexed in situ single-cell profiling of human brain

Authors: *V. M. RACHLEFF[1], A. BAHRAMI[2], A. BOSWORTH[2], C. PHAN[2], A. WARDHANI[2], A. ROSENBLOOM[2], J. BEECHEM[2], C. D. KEENE[1];
[1]Univ. of Washington, Seattle, WA; [2]NanoString Technologies, Seattle, WA

Abstract: Human brain aging is a complex process that follows a widely varied course, from healthy aging to devastating age-related neurodegenerative pathologies. While epidemiological advances and general health have improved outcomes to an extent, pathways responsible for healthy brain aging, and those that divert these processes, are largely unknown. Accumulation of pathologic proteins is the primary indicator of the initiation and progression of degeneration, which results in the loss of specific cell types in select brain regions. While single-cell RNA sequencing has enabled the characterization of precisely which cell types are selectively vulnerable in disease, the approach lacks both pathological protein and spatial context which are essential to address the fundamental question of *why* certain cell types are vulnerable. This relationship between pathology and cell-type specific selective vulnerability remains unknown for most neurodegenerative diseases; multiplexed spatial omics approaches have the potential to fill this critical knowledge gap. The CosMx™ Spatial Molecular Imager introduces highly multiplex protein and >6000 plex RNA multiomic exploration of FFPE tissues. For spatial omics applications, it is critical to focus efforts across transitional zones (one or more cortical gyri), but

high plex cycling imagers are limited to 100-300 mm^2 of imaging area, insufficient to study neurodegeneration across anatomical boundaries. Here we present a novel application of a Large Surface Area flow cell with > 1600 mm^2 of imaging area, a > 5-fold increase. Alzheimer's disease (AD) is the most common cause of dementia and is characterized by a stereotypical spatiotemporal progressive deposition of pathologic peptides, amyloid beta (Aβ) and phosphorylated tau (pTau). pTau burden, in the form of neurofibrillary degeneration, corresponds strongly with cognitive impairment and progresses from medial temporal lobe structures to neocortex. The Large Surface Area CosMx approach enables the study of AD progression akin to the earliest whole mount studies pioneered by Braak and colleagues, but at unprecedented resolution. Here we update our progress, presenting a spatial transcriptomic analysis of AD particularly with respect to critical regional junctures as a strategy to capture cross-regional spatiotemporal progression of pathology in the context of cell-specific vulnerability. Advances in spatial omics technologies support development of a more comprehensive understanding of AD at a molecular level and help disentangle the relationship between cell-specific vulnerability and underlying pathologic mechanisms of neurodegeneration.

Disclosures: **V.M. Rachleff:** None. **A. Bahrami:** A. Employment/Salary (full or part-time):; Nanostring Technologies. **A. Bosworth:** A. Employment/Salary (full or part-time):; Nanostring Technologies. **C. Phan:** A. Employment/Salary (full or part-time):; Nanostring Technologies. **A. Wardhani:** A. Employment/Salary (full or part-time):; Nanostring Technologies. **A. Rosenbloom:** A. Employment/Salary (full or part-time):; Nanostring Technologies. **J. Beechem:** A. Employment/Salary (full or part-time):; Nanostring Technologies. **C.D. Keene:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.19/C6

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

Support: F31AG084330
R01AG078859

Title: Retrotransposon transcripts in single-nucleus RNA-seq data on Alzheimer's disease patients: relevance to clinical-pathological measures

Authors: *C. M. MCENTEE[1,2], T. J. LAROCCA[1,2];
[1]Hlth. and Exercise Sci., Colorado State Univ., Fort Collins, CO; [2]Center for Healthy Aging, Colorado State University, Fort Collins, CO

Abstract: Alzheimer's disease (AD) is a complex neurodegenerative disease involving many cell type-specific changes, and recent work has investigated the pathogenesis of AD using single-nucleus RNA sequencing (snRNA-seq) to characterize AD-related changes in gene expression in individual cells. These studies have focused on protein coding genes, but increasing evidence

suggests that non-coding RNAs, including from transposable elements (TEs), may play a role in AD. TEs consist of transposons and retrotransposons (DNA sequences that propagate in the genome via “cut-and-paste” or “copy-and-paste” mechanisms, respectively). Our laboratory and others have shown that TE *transcripts* are elevated with AD in bulk RNA-seq data and are associated with AD pathology and neuroinflammation. To determine if these observations reflect cell type-specific changes in the brain, we first reanalyzed a benchmark snRNA-seq dataset for cell-specific changes in TE transcript expression relating to AD and/or AD pathology using the SoloTE pipeline. Consistent with previous analyses of these data, we identified 64,760 cells from 48 prefrontal cortex samples that could be classified into seven major brain cell types, and we found a general increase in total TE transcripts in all cell types in samples from subjects with high pathology. Two active retrotransposon transcripts, LTR5-Hs and L1HS, both of which have been linked with aging and pro-inflammatory signaling, were particularly elevated in excitatory neurons, and transcript levels of both retrotransposons correlated with markers of amyloid beta pathology and cognitive function. We then examined transcriptional accessibility of these and other TEs in a second dataset, which included single-nucleus chromatin profiling data, and we found an increase in the number of TEs within accessible chromatin regions of the genome in excitatory neurons of AD subjects. Together, these data suggest that transcriptional and epigenetic changes in excitatory neurons may be central to the TE dysregulation observed in prior bulk sequencing studies. To expand on these findings, we are: 1) analyzing additional snRNA-seq datasets on brain aging and AD; and 2) determining if key TE transcripts are associated with differences in tau and other age/AD-related pathologies.

Disclosures: C.M. McEntee: None. **T.J. LaRocca:** None.

Poster

PSTR012: Alzheimer’s Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.20/C7

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

Support: R01AG075069

Title: A novel technique for monitoring Alzheimer’s disease associated changes in brain-derived extracellular vesicle cargos in mouse models.

Authors: *M. ALAM, M. A. OSTACH, N. F. FITZ;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Extracellular vesicles (EVs) are lipid membrane-delimited nano vesicles secreted by almost all cell types into extracellular spaces and contain important cargo including noncoding RNAs. Brain-derived EVs are collectively released by all neural cells and are emerging as key mediators of communication and potentially contribute or served as biomarkers for neurodegeneration. However, to gain a more comprehensive understanding of brain-derived EVs

role in different neurodegenerative conditions it is important to overcome limitations in current EV sampling and isolation techniques. Therefore, to better sample and analyze brain-derived EVs, we developed a novel in vivo microdialysis technique which allows for real time collection from the brain interstitial fluid (ISF) where EVs are directly released, allowing for characterization of EVs cargo and correlation with disease phenotype in Alzheimer's disease model mice. We applied a novel Cerebral Open Flow Microdiyalysis (cOFM) method for collecting EVs from the hippocampal ISF (ISF-EV) of awake freely moving mice and subsequently isolated EVs from ISF, plasma and brain tissues in wild-type (WT) and APP/PS mice for compartment specific characterization. Small noncoding RNAs (ncRNAs) were isolated from the EVs, sequenced and data analyzed using COMPSRA, pipeline for ncRNAs. We identified a significant number of differentially expressed ncRNAs transcripts when comparing ISF-EV and plasma-EV suggesting unique populations of EVs were isolated from the two sample types. Further, we determined unique profiles of ISF-EV specific ncRNAs in APP/PS mice compared to WT mice, which were associated with amyloid pathology. Thus, the novel cOFM technique will be a important method to sample brain-derived EVs and could be used to better understand changes in EV cargos associated with a number of neurodegenerative diseases.

Disclosures: **M. Alam:** None. **M.A. Ostach:** None. **N.F. fitz:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.21/C8

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

Support: P01AG073082

Title: Bridging single-nucleus transcriptomic profiles with neural network functions and locomotor behaviors in an Alzheimer's Disease mouse model

Authors: ***F. JIANG**[1], S. R. MILLER[2], J. PAN[3], A. AGRAWAL[2], P. HONMA[4], J. SHIN[2], D. XIA[5], P. SANCHEZ[5], R. THOMAS[2], I. COBOS[3], J. J. PALOP[4];
[1]Univ. of California, San Francisco, San Francisco, CA; [2]Gladstone Inst., San Francisco, CA; [3]Stanford Univ., Stanford, CA; [4]Gladstone Inst., UCSF, San Francisco, CA; [5]Denali Therapeut., South San Francisco, CA

Abstract: Alzheimer's Disease (AD) is a neurodegenerative disease characterized by pathological protein deposits in the brain, including amyloid plaques and neurofibrillary tangles. AD patients show disease-associated transcriptomic alterations in a cell-type-specific manner and display aberrant brain network activities, which eventually leads to behavioral deficits. However, few studies have revealed the relationship between transcriptomic expression at single cell resolution, neural network dynamics, and behavioral activity. To systematically investigate how variations in transcriptomic profiles interact with neural network dynamics, we performed

single-nucleus RNA sequencing (snRNA seq) on dissected hippocampi sections from AD knock-in (App KI) mice (n=39) following 14-day continuous telemetric electroencephalography recording which included a readout of mouse locomotor activity. We identified and quantified disease alterations in theta and gamma band power and detected multiple types of epileptiform activities in male and female KI mice, and we observed nocturnal locomotor hyperactivity specifically in female KI animals. Using the snRNA seq data, we found differentially expressed genes in major cell type including interneurons, oligodendrocytes, astrocytes, and microglia, corresponding to locomotive hyperactivity, gamma power alterations, and epileptiform spikes, and performed functional analysis to show potential proteomic pathways relevant to neural network dynamics. Our study provides new insights on the mechanistic relationships connecting behavioral alterations, network dysfunction, and transcriptomic variations, and may support the development of treatments for AD.

Disclosures: F. Jiang: None. **S.R. Miller:** None. **J. Pan:** None. **A. Agrawal:** None. **P. Honma:** None. **J. Shin:** None. **D. Xia:** None. **P. Sanchez:** None. **R. Thomas:** None. **I. Cobos:** None. **J.J. Palop:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.22/C9

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

Title: Netsseq provides deep molecular insight into astrocyte biology and identifies complex regional and state dependent heterogeneity in the human brain.

Authors: *C. UGBODE, G. BAYRAKTAR, M. LIZIO, X. XU, B. OSSOLA, J. POWELL, D. CADWALLADR, T. THOMPSON, J. LAWRENCE, S. SHEARDOWN, K. PAGE, M. CARLTON, N. L. BRICE, L. A. DAWSON;
Cerevance Ltd, Cambridge, United Kingdom

Abstract: Neurodegenerative diseases remain a major challenge in drug discovery. To identify new, disease modifying treatments, an integrated understanding of individual cell types, their function and how their properties change during disease is required. Cerevance's proprietary technology platform, NETSseq, was developed to provide deep molecular understanding, by examining the expression of >12,000 genes, at the individual cell type level, across multiple structures in the human brain. We deployed this technique to assess transcriptomic changes in astrocytes from different regions of the brain as well as to understand how astrocytes change during disease.
Using post-mortem human brain samples from donors with Alzheimer's Disease (AD) and non-degenerative disease age-matched controls, we have identified astrocyte-specific genes that change across the spatial and temporal continuum of AD, along with two astrocyte signatures that represent different states of glial activation. Pathway analyses show that disease changes are

enriched for several processes, including redox homeostasis. Notably, Metallothionein 2A (MT2A), a small cysteine-rich antioxidant, is significantly increased in AD astrocytes in the parietal and middle temporal cortices (more resilient regions in AD), but not in the entorhinal cortex (vulnerable region in AD). These results suggest that even in disease, astrocytes may play an important role in neuroprotection, although these protective capabilities may vary across regions.
Along with generating highly reproducible molecular profiles from specific CNS cell types, NETSseq also enables the understanding of spatial dynamics across the astrocyte transcriptome, thereby identifying relevant pathways and genes to target for the development of novel therapies.

Disclosures: C. Ugbode: None. **G. Bayraktar:** None. **M. Lizio:** None. **X. Xu:** None. **B. Ossola:** None. **J. Powell:** None. **D. Cadwalladr:** None. **T. Thompson:** None. **J. Lawrence:** None. **S. Sheardown:** None. **K. Page:** None. **M. Carlton:** None. **N.L. Brice:** None. **L.A. Dawson:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.23/C10

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

Title: Stratifying of Alzheimer's disease leads to the identification of actively protective biologies

Authors: *C. NAVARRON IZQUIERDO, A. MALINOWSKI, M. SANNA, K. TAYLOR, S. DAS, S. HOGG, C. STUBBERFIELD;
PrecisionLife Ltd, Oxford, United Kingdom

Abstract: Alzheimer's disease (AD) is a complex, multifactorial disease, characterised by a high degree of heterogeneity. GWAS have identified several disease-associated genes, but these findings have not translated into progress in clinical trials. This likely reflects the limitations of GWAS in identifying links to only single variants, while the key to understanding complex diseases is to find combinations of interacting variants that drive disease risk and define patient subgroups. The PrecisionLife (PL) platform utilises a hypothesis-free method for detection of combinations of features that together strongly associate with variations in disease risk, symptoms, and therapy response. Patient stratification insights generated enable identification of mechanistic subgroups with accompanying genetic biomarkers, which are likely to respond to specific treatments. PL previously examined a genomic dataset from the UK Biobank and identified known and novel risk factors that formed the basis of six subgroups of AD patients with distinct mechanistic aetiologies. To confirm these findings in an independent cohort and extend our stratification insights, we analysed the ROSMAP dataset (https://dss.niagads.org/cohorts/religious-orders-study-memory-and-aging-project-rosmap/). With the greater clinical detail and additional omics data available in ROSMAP, we were able to

identify patient subgroups defined by clinical phenotypes, and linked their genetic signatures with gene expression patterns. Identification of new targets for AD therapies can benefit from understanding both disease-causative and -protective biology. However, the latter have not been explored by standard genetic approaches. To explore actively protective biology of AD, PL identified a cohort of patients with multiple risk factors from the results of causative disease analyses. This high-risk cohort was used to identify actively protective SNP signatures enriched in individuals who remain healthy despite high genetic risk. Combinatorial analyses reveal novel disease-causative and -protective biological pathways. Therapeutic modulation of these, matched with the associated genetic biomarkers, will form the basis for precision medicine approaches in AD.

Disclosures: C. Navarron Izquierdo: A. Employment/Salary (full or part-time):; PrecisionLife Ltd. **A. Malinowski:** A. Employment/Salary (full or part-time):; PrecisionLife Ltd. **M. Sanna:** A. Employment/Salary (full or part-time):; PrecisionLife Ltd. **K. Taylor:** A. Employment/Salary (full or part-time):; PrecisionLife Ltd. **S. Das:** A. Employment/Salary (full or part-time):; PrecisionLife Ltd. **S. Hogg:** A. Employment/Salary (full or part-time):; PrecisionLife Ltd. **C. Stubberfield:** A. Employment/Salary (full or part-time):; PrecisionLife Ltd.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.24/C11

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

Support: NIH-R01-AG75818

Title: Data-independent acquisition proteomic approach reveals calcium-activated potassium channels and ADP-ribosylation factors are linked to cognitive resilience to Alzheimer's disease

Authors: *Y. CHEN[1], L. A. FISH[1], T. STEVENSON[1], M. C. SAUL[2], N. HADAD[3], A. DUNN[2], V. M. PHILIP[2], S. CANCHI[1], C. C. KACZOROWSKI[4];
[1]Dept. of Neurol., Univ. of Michigan, Ann Arbor, MI; [2]The Jackson Lab., Bar Harbor, ME; [3]The Jackson Lab., Bar Habor, ME; [4]Dept. of Neurol., The Univ. of Michigan, Ann Arbor, MI

Abstract: An individual's genetic makeup plays a significant role in determining the resilience/susceptibility to Alzheimer's disease (AD). Although advances in genetics have significantly enhanced our understanding of inheritable risk factors for AD, the ultimate biological effectors of AD genetic and environmental risk are often proteins and metabolic pathways they modulate. Identification of these effector proteins will provide new insights into mechanisms contributing to the variability in susceptibility to impaired cognitive function in AD. To this end, we took an unbiased data-independent acquisition (DIA) liquid chromatography mass spectrometry (LC-MS) proteomics approach to measure in-depth coverage of protein abundance at the whole proteome level of prefrontal cortex on a genetically diverse AD mouse

population (AD-BXD), a translationally relevant panel that models the extensive variability in human cognitive decline progression. We used a novel quantitative metric for determining cognitive resilience along a continuum. A linear regression analysis of contextual fear memory performance in AD-BXD strains compared to their Ntg-BXD counterparts was performed. A residual, or the numerical deviation from linear regression line of best fit for a given strain, was then calculated; we defined this residual as "resilience trait". Correlation analysis between protein abundance and this quantitative resilience trait has identified several candidate proteins associated with early onset AD resilience (KCNN1 & 2) and late-stage AD (ADP-ribosylation factors). Additionally, weighted protein co-expression network analysis (WPCNA) was performed to assess whether there are any co-expressed protein modules were significantly associated with the resilience trait. We discovered a cluster of co-expressed vascular-and blood-related proteins that regulate protease and hydrolase activity to be negatively associated with the resilience trait at early onset stages of AD, and a group of keratin proteins to be positively associated with the resilience trait at later stages of AD. In summary, our work reveals novel proteomic disease-related changes associated with cognitive resilience to AD that has not been observed at transcriptomic level.

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Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

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Program #/Poster #: PSTR012.25/C12

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

Support: NIA RO1 To TRP: 1ro1ag082135

Title: Microrna stability and degradation rates are altered in the hippocampus of a mouse model of Alzheimer disease

Authors: *K. MENDEZ[1,2], B. VISSER[3], S. FLURY[3], M. NEWBY[3], Y. NGAI[3], A. HARTOUN[3], T. R. PAK[3];
[1]Loyola Univ. Chicago, Chicago, IL; [2]Loyola University Chicago Stritch School of Medicine, Chicago, IL; [3]Loyola Univ. Chicago Stritch Sch. of Med., Chicago, IL

Abstract: microRNA stability is tissue and cell type specific, and there is wide variability among different microRNA species. For example, many microRNAs are rapidly degraded in primary neurons and in multiple brain regions, while others have long half-lives in these same cell types and in astrocytes. Our earlier studies showed that the rate of degradation was brain-region specific, dependent on age, and altered by the steroid hormone, 17b-estradiol (E_2). Others have shown that mature microRNA expression levels are altered with advanced age, and are

dysregulated in age-related diseases, such as Alzheimer Disease (AD). There is also a female bias in AD, as women are more likely to be diagnosed and experience faster disease progression than men. Therefore, we hypothesized that (1) microRNA degradation in the brain would be altered in AD, and (2) these altered degradation rates might be abolished with E_2 treatment because E_2 is neuroprotective. To test our hypothesis, we used brain tissue from transgenic mice (3xTg-AD: APPswe, MAPTP301L, PS1knock-in). Female mice (12 weeks) were ovariectomized (OVX) to remove endogenous E_2. One week or four weeks after OVX, females were treated with E_2 (2.5 ug/kg) or safflower oil (vehicle), once a day per 3 days to mimic conditions of "early" or "late" hormone replacement therapy in women. The hypothalamus, hippocampus, and prefrontal cortex were microdissected, homogenized and incubated with ^{32}P-labeled oligonucleotide sequences for miR-9-5p, miR-181a-5p, and miR-495 to measure the rate of degradation in each brain region. Our results showed that the stability of all three miRNAs assessed changed in AD model. In the hippocampus, all miRNAs degraded faster in the AD model compared to WT at 3 months old, prior to overt signs of disease pathology. These results suggest that microRNA stability could be an early marker of AD, and contributes to the progression of the disease

Disclosures: K. Mendez: None. **B. Visser:** None. **S. Flury:** None. **M. Newby:** None. **Y. Ngai:** None. **A. Hartoun:** None. **T.R. Pak:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.26/C13

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

Support: NIA RF1AG057553

Title: A phosphoproteomic analysis to elucidate the mechanism of action of CT1812 in Alzheimer's disease

Authors: *E. CHO[1], K. PANDEY[2], D. DUONG[3], N. T. SEYFRIED[3], A. O. CAGGIANO[4], V. DI CARO[1], M. E. HAMBY[1];
[1]Cognition Therapeut., Inc., Pittsburgh, PA; [2]Emory Univ., Atlanta, GA; [3]Emory Univ. Sch. of Med., Atlanta, GA; [4]Cognition Therapeut., Inc., New York, NY

Abstract: The sigma-2 receptor (S2R) modulator CT1812 is a first-in-class investigational therapeutic, currently in Phase 2 clinical trials for Alzheimer's disease (AD). Preclinical and clinical studies have shown that CT1812 displaces Aβ oligomers from synapses and clears them from the brain into the cerebrospinal fluid (CSF), restoring cognitive performance in a transgenic mouse model of AD. To investigate the mechanism of action (MoA) of CT1812, a phosphoproteomic analysis of CSF samples from the phase 2 clinical study SPARC was performed. SPARC (COG0105; NCT03493282) was a single-center, Phase 1/2, randomized, double-blind, placebo-controlled, parallel group trial in adults with mild to moderate AD to

assess the safety and tolerability of two doses of CT1812 (100 mg and 300 mg) vs. placebo for 6 months (N=23). Immobilized metal affinity chromatography (IMAC) phosphoproteomics were performed on baseline and on 6 months CSF samples (N=17, treatment compliant). The protein-protein interaction (PPI) map was built using STRING pathway analyses (v12.0) using a list of phosphoproteins ($p \leq 0.05$). To visualize the S2R components' interactions with these altered phosphoproteins, S2R complex proteins TMEM97, PGRMC1, PRNP (PrP^c) and LDLR were manually added. A total of 303 phosphopeptides were significantly altered in SPARC CSF, 35 phosphopeptides from 23 proteins ($p \leq 0.1$, including 18 phosphopeptides from 13 proteins ($p \leq 0.05$)). Among the identified phosphoproteins, APOE, SPP1, APOL1, CHGB, and SPARCL1 ($p \leq 0.05$) were AD-relevant. Using STRING, a PPI map of these five phosphorylated proteins plus the S2R complex proteins showed connections underlying their role in CT1812 S2R mediated MoA: "endoplasmic reticulum (vesicle)", "amyloid-beta binding", "regulation of amyloid fibril formation", and "lipoprotein metabolic process". Closer examination at the single residue phospho-site level identified specific phospho-sites, some of which have known functional roles. Data for all sites be presented in poster form. Of particular note, phosphorylated APOE on T212 was decreased in CT1812 treated group compared to placebo. APOE T212A, a non-phosphomimic, has been studied for its ability to bind amyloid β, reducing avidity for Aβ42. Of note, this site was also regulated by treatment with CT1812 in an interim analysis from an independent cohort, SHINE-A. Given the MoA of CT1812 and the relevance of APOE to Aβ and AD, this is an interesting finding worthy of future study to unravel further the potential biological effect of CT1812 on APOE biology, which could facilitate learnings important to the clinical development of CT1812.

Disclosures: E. Cho: None. **K. Pandey:** None. **D. Duong:** None. **N.T. Seyfried:** None. **A.O. Caggiano:** None. **V. Di Caro:** None. **M.E. Hamby:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

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Program #/Poster #: PSTR012.27/C14

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

Support: Hevolution/American Federation for Aging Research
National Institute on Aging RO1AG068293
Cure Alzheimer's Fund
Alzheimer's Drug Discovery Foundation

Title: Highest plex spatial multiomics as a discovery tool for senescence cell biology in Alzheimer's disease

Authors: *H. R. HUDSON[1], T. C. ORR[2], A. ROSENBLOOM[3], J. BEECHEM[3], M. E. ORR[2,4]; [1]Translational Neurosci., Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [2]Intrnl. Med.

Geriatrics and Gerontology, Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [3]NanoString Technologies (a Bruker company), Seattle, WA; [4]Salisbury VA Medical Center, Salisbury, NC

Abstract: Cellular senescence is a complex stress response that contributes to chronic inflammation and neuron loss in many neurodegenerative diseases. Our team identified that neurons with intraneuronal tau deposition as neurofibrillary tangles (NFTs) exhibit cellular senescence phenotypes in postmortem human Alzheimer's disease (AD) brain tissue. Senescent cells constitute ~ 2% of the total cell population in AD brains. Senescent cells are notorious for negatively impacting their surrounding environment by the molecules they release. We are interested in understanding the spatial relationship among senescent cells, tau neuropathology and disease progression. This project aims to elucidate if specific phospho-tau species contribute to senescence and AD pathology. The advancement of spatially resolved, multiplex proteomic and transcriptomic technologies has revolutionized and redefined the approaches to study tissue heterogeneity, microenvironments, cellular interactions, cellular diversity, and therapeutic response. Spatial transcriptomics has traditionally led the way in plex. However, multiple studies have demonstrated poor correlations between RNA expression and protein abundance, owing to transcriptional and translational regulation, target turnover, and most critically, post-translational protein modifications. A more holistic, ultra-high-plex, and high-throughput proteomic atlas approach becomes critical for the next phase of discovery biology. The GeoMx Digital Spatial Profiler platform is uniquely suited to support high-plex proteomics. The platform allows for the simultaneous analyses of proteins from discrete regions of interest (ROIs) in tissue sections while preserving spatial context. The assay relies upon Abcam antibodies coupled to photocleavable DNA barcodes readout with NGS sequencing, allowing for theoretically unlimited plex. Here we introduce the Human Immuno-Oncology Proteome Atlas (IPA), a 570+ antibody-based proteomic discovery panel, compatible with immunohistochemistry on formalin fixed paraffin embedded (FFPE) tissues with NGS readout, coupled with a 44 plex neuropathology custom antibody panel and a Whole Transcriptome RNA panel. In summary, this project uses a barrier-breaking, highest plex spatial multi-omics solution to explore the role of senescence in AD progression. The ability to pair highly multiplexed exploration of phosphorylated tau species with transcriptomic profiling reveals new insights into potential roles of specific phospho-tau species on cellular senescence and disease progression.

Disclosures: H.R. Hudson: None. **T.C. Orr:** None. **A. Rosenbloom:** A. Employment/Salary (full or part-time):; Nanostring Technologies Inc, Bruker. E. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nanostring Technologies Inc, Bruker. **J. Beechem:** A. Employment/Salary (full or part-time):; Nanostring Technologies Inc, Bruker. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nanostring Technologies Inc, Bruker. **M.E. Orr:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.28/C15

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

Title: High-resolution mass spectrometry imaging reveals region- and cell-type-specific molecular changes in the brains of Alzheimer's disease mice

Authors: *B. GURDON[1,2], T. ZHAO[1], A. DUNN[1], T. STODOLA[1], K. O'CONNELL[1,2,3], B. HOFFMANN[1];
[1]The Jackson Lab., Bar Harbor, ME; [2]The University of Maine, Orono, ME; [3]Tufts University, Medford, MA

Abstract: Alzheimer's disease (AD) involves widespread molecular changes throughout the brain that begin well before clinical symptom onset. Identifying and quantifying these changes can provide valuable insights into developing potential therapeutic targets for AD; however, previous approaches in both mouse models and humans have relied heavily on limited brain regions or end-stage disease processes. Many of these studies have focused on transcriptomic changes, yet it is increasingly clear that transcript and protein levels can be highly discordant, particularly in the brain with aging and disease. Moreover, defects in proteostasis may be a common feature of aging and AD, further exacerbating the discordance between the transcriptome and proteome, and highlighting the need to better understand the impact of age and disease on protein expression to uncover processes associated with disease progression and cognitive decline. Here, we have employed mass spectrometry imaging (MSI) to identify and quantify thousands of peptides, lipids, and metabolites with cellular spatial resolution at prodromal (2-4 months), onset (12-14 months), and late-disease states (18+ months) in both male and female, AD and wild-type mice. This approach overcomes the limitations of other single-cell methods and maintains the highly compartmentalized organization of neurons (e.g., distal dendrites or axon terminals), allowing us to evaluate region-specific patterns of peptides, lipids, and metabolites. Through protein pathway analysis and annotation and quantification of lipids and metabolites, we have observed significant alterations in the hippocampal and cortical peptidome, lipidome, and metabolome between disease stages. Intriguingly, these changes are highly cell- and region-specific, pointing to heterogeneous cell vulnerabilities in AD. This is the first study of its kind to generate an 'omics "atlas" of the AD brain; in combination with other single-cell approaches, it will contribute to a deeper understanding of molecular events leading to AD progression, as well as identify novel therapeutic targets that may be leveraged in early or late disease stages to improve clinical outcomes.

Disclosures: B. Gurdon: None. **T. Zhao:** None. **A. Dunn:** None. **T. Stodola:** None. **K. O'Connell:** None. **B. Hoffmann:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.29/C16

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

Title: Elucidating regulators of neuroinflammation and neuronal death in Alzheimer's disease.

Authors: *H. TRAN;
Houston Methodist Res. Inst., Houston, TX

Abstract: Elucidating regulators of neuroinflammation and neuronal death in Alzheimer's disease.

AuthorsHan Nhat Tran[1,2], Thomas Wong[1], Fransisca Leonard[1], Ali Faridar[1], Kristin Huntoon[3], Kyuson Yun[1,2]
[1]Department of Neurology, Houston Methodist Research Institute, Houston, TX, USA. [2]Department of Neurology, Weill Cornell Medical College, New York, NY, USA. [3]Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA, USA

Disclosures

H.N. Tran: None. **T. Wong**: None. **F. Leonard**: None. **A. Faridar**: None. **K. Huntoon**: None. **K. Yun**: K.Y. is a co-founder of EMPIRI, Inc

Abstract

While studies of neurodegenerative diseases, such as Alzheimer's disease (AD), were mostly focused on neural cells in the past, emerging studies highlight the importance of neuroinflammation and the immune system in disease initiation and progression. Therefore, elucidating specific pathways responsible for aberrant inflammatory responses in AD patients and other neural injury will advance our ability to develop effective, novel neuroprotective treatments. My project is focused on elucidating aberrantly activated or suppressed signaling molecules and identifying cell types responsible for their expression in the blood and brain of AD patients. We are also leveraging our expertise in single cell genomics and neuroinflammation in brain cancer patients, who have the opposite phenotype with highly suppressed immune response in the brain. I am analyzing PBMCs from age- and sex-matched healthy donors (n = 6), AD patients (n = 2), and GBM patients (n = 5) using single-cell Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-Seq). Preliminary analysis of our CITE-seq data show different clustering patterns in Antibody-Derived Tags (ADT) vs. RNA based analysis and unique clusters when both are combined in Weighted Nearest Neighbor (WNN) analysis. I am currently integrating transcriptomic and proteomic analyses to define common and distinct immune cell phenotypes/states in AD vs. GBM patients and identifying the most differentially regulated pathways and cell types between healthy vs. AD and AD vs. GBM patients. In addition, I will investigate differences in cell-cell communications as consequences of differential cytokine/chemokine expression and expansion/contraction of different immune cell types in circulation in different disease states. Through these analyses, I will define cell surface markers associated with aberrantly activated immune cells in AD and identify potential therapeutic targets to normalize hyper-activated immune responses in the brain and blood, with a goal of providing neuroprotective treatments for AD patients.

Disclosures: H. Tran: None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.30/C17

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

Support: NIH Grant K00AG080847

Title: Higher gene expression of dynein heavy chains in the dorsolateral prefrontal cortex predict lower neuropathology burden and better cognitive outcomes in individuals with alzheimer's disease

Authors: *E. M. LUCERO[1], T. BRUNETTI[1], H. J. CHIAL[2], H. POTTER[3], C. GIGNOUX[1]; [1]Biomed. Informatics, Univ. of Colorado, Aurora, CO; [2]Neurol., Univ. of Colorado Alzheimer's and Cognition Ctr., Dept. Neurol., Linda Crnic Inst. for Down Syndrome, Univ. of Colorado Anschutz Med. Campus, Aurora, CO; [3]Dept. of Neurol., Director, Alzheimer's and Cognition Ctr., Aurora, CO

Abstract: Motor proteins play a key role in neuronal functions and morphology that are important for learning and memory. We have previously reported that increased expression *KIF11/*Kinesin-5 overrides amyloid-mediated Alzheimer's disease (AD) phenotypes in a mouse model, effectively maintaining cognitive function in the face of amyloid beta pathology. Additionally we reported that higher expression in AD human subjects was associated with better cognitive outcomes. Here, we evaluated the association of key AD phenotypes with mRNA expression levels of a select set of Dynein motor proteins. We utilized measurements of gene expression, AD neuropathology burden, and cognition provided by the ROS/MAP study to determine whether an association exists between AD phenotypes and brain expression of genes for cytoplasmic and axonemal dynein heavy chains. Neuropathology burden was determined through immunohistochemistry. Z-scores from the raw scores of 19 cognitive tests were used to determine global cognition. Neuropathology burden and global cognition measurements were provided by Rush Alzheimer's Disease Center. Measurements of gene expression in the dorsolateral prefrontal cortex (DLPFC) (n=634) were determined through an established RNAseq analysis pipeline (Logsdon et al., 2019, syn8456638; syn8456629) and made available to us through the Accelerating Medicines Partnership in Alzheimer's Disease Target Discovery and Preclinical Validation knowledge portal (syn3219045). Associations of gene expression with neuropathology and cognition were determined through multiple linear regression and mixed effects models covarying for age, sex, education, and post-mortem interval. In participants with AD (CERAD score > 2), higher gene expression levels of *DYNC1H1* and *DNAH1* in the DLPFC predicted better cognitive performance longitudinally (p=0.03 and p=0.00197, respectively) and at the last visit prior to death (p=8.701e-05 and p=3.571e-05, respectively). Higher expression of *DYNC1H1* and *DNAH1* were also associated with lower amyloid pathology (p=0.0001257 and p=2.356e-07, respectively) and tau tangles (p=2.356e-07 and p=2.659e-09, respectively). Our finding that AD participants with higher expression levels of *DYC1H1* and *DNAH1* show reduced cognitive decline and decreased AD pathology suggest a potential beneficial effect of these motor proteins on AD progression. Based on the functions of these motor proteins, these findings warrant further studies to identify potential mechanisms underlying this association.

Potential mechanisms include facilitation of higher rates of phagocytosis or neuronal lysosomal degradation of amyloid beta.

Disclosures: E.M. Lucero: None. **T. Brunetti:** None. **H.J. Chial:** None. **H. Potter:** None. **C. Gignoux:** None.

Poster

PSTR012: Alzheimer's Disease: Genomics and Other Omics Approaches I

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.31/C18

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

Support: TUBITAK (Scientific and Technological Research Council of Turkey)

Title: The Modifications in Hippocampal Lipids and Neuronal Density in an Alzheimer's Disease Model

Authors: E. N. KESKINOZ[1], ***E. TOKLUCU**[1], K. BIRISIK[1], M. ÇELIK[1], M. BILGIN[2], N. TOM[2], E. ULUPINAR[3], D. ÖZ ARSLAN[1];
[1]Acibadem Mehmet Ali Aydinlar Univ., Istanbul, Turkey; [2]Danish Cancer Inst., Copenhagen, Denmark; [3]Anat. and Interdisciplinary Neurosci., Northwestern Univ., Chicago, IL

Abstract: Alzheimer's disease (AD) is a neurodegenerative disease characterized by neuronal membrane degeneration, and neuronal loss. Lipids, especially phospholipids, which are abundant in the brain and protect the integrity and function of neuronal membranes, are thought to be damaged during the progression of AD. The main purpose of the study is to investigate the effect of choline, fish oil, and uridine-5'-monophosphate (UMP) supplementation on lipid profiles in the 5XFAD mouse model of AD, and to characterize cholesterol, lysophospholipids (lyso GPLs), glycerophospholipids (GPLs), sphingolipids (SLs), and lysophospholipid acyltransferases (lyso GPL O-ATs), glycolipids (GLs), glycerophospholipid (GPL Os), and neuron density in hippocampal areas dentate gyrus (DG), CA1 and CA3. Lipidomic analysis was conducted on hippocampal brain tissue specimens from 3-, 6-, and 9-month-old 5XFAD mice and littermate controls utilizing cutting-edge mass spectrometer with direct infusion (shotgun lipidomics) and LC-MS techniques. Cresyl violet staining was used to measure neuron density in the hippocampal regions (DG, CA1 and CA3) of brain tissue sections. In comparison to non-transgenic controls, 5XFAD transgenic mice showed significant differences in cholesterol, GPLs, SLs, GLs, lyso GPLs, lyso GPL O-ATs, and GPL Os. Cresyl violet-stained sections also revealed significant differences in neuron density in the hippocampal region. Our data suggest that choline, fish oil, and UMP supplementation may affect lipid profile and neuronal density on the hippocampal tissues of AD. The study emphasizes the significance of understanding the link between lipid homeostasis, neuronal loss, and cognitive impairment in Alzheimer's disease will help to identify new therapeutic approaches for AD.

Disclosures: **E.N. Keskinoz:** None. **E. Toklucu:** None. **K. Birisik:** None. **M. Çelik:** None. **M. Bilgin:** None. **N. Tom:** None. **E. Ulupinar:** None. **D. Öz Arslan:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.01/C19

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

Support: ITALIAN MINISTRY OF HEALTH (RF-2018-12365391)

Title: Long-term administration of ultra-micronized PEA alters disease progression in the Tg2576 mice and reveals neuroprotective effects on behavior, brain morphology and biochemistry.

Authors: ***D. DECANDIA**[1,2], A. PANUCCIO[2], D. CUTULI[3,2], D. TORTOLANI[4,2], L. LA BARBERA[5,2], E. C. LATAGLIATA[2], F. CIARAMELLANO[2], L. SCIPIONI[6,2], G. GIACOVAZZO[7,2], R. COCCURELLO[8,2], S. ODDI[7,2], M. MACCARRONE[6,2], L. PETROSINI[2]; [1]Dept. of Psychology, PhD program in Behavioral Neuroscience, Sapienza Univ. of Rome, Rome, Italy; [2]IRCCS Santa Lucia Fndn., Rome, Italy; [3]Dept. of Psychology, Sapienza Univ. of Rome, Rome, Italy; [4]Univ. degli Studi di Bari, Dept. di Farmacia Scienze del Farmaco, Bari, Italy; [5]Dept. of Med. & Surgery, Univ. Campus Bio-Medico di Roma, Rome, Italy; [6]Dept. di scienze cliniche applicate e biotecnologie, Univ. degli studi dell'Aquila, L'Aquila, Italy; [7]Dept. di Medicina Veterinaria, Univ. degli Studi di Teramo, Teramo, Italy; [8]Inst. for Complex Systems (ISC), Natl. Council of Res. (CNR), Rome, Italy

Abstract: Alzheimer's disease (AD) is the most common cause of dementia and yet, effective pharmacological therapies are missing. Neuroinflammation plays a crucial role in AD progression, prompting research into the modulation of the immune system as an innovative therapeutic strategy. Thus, identification of novel targets restraining neuroinflammation is crucial to prevent or delay disease progression. Palmitoylethanolamide (PEA) is an emerging nutraceutical compound with high efficacy/risk ratio and lack of tolerance induction and interference with other pharmacological therapies. PEA is an endogenous N-acylethanolamine that acts as bioactive lipid mediator, and is biochemically and functionally related to the endocannabinoid system. PEA is produced by neurons, microglia and astrocytes in responses to various damaging processes, with an overall pro-homeostatic role. Preclinical studies showed the anti-inflammatory, pain-relieving, and neuroprotective actions of ultra-micronized (um) PEA, a formulation that favors its bioavailability. The present study aims at evaluating the neuroprotective potential of chronic umPEA treatment via 6-month subcutaneous pellets on learning, memory and motivation (by Novel Object Recognition Test and Conditioned Place Preference), synaptic plasticity, neuroinflammation, and oxidative stress in 12-month-old Tg2576 (Tg) mice (from 6 to 12 months of age), a widely used AD mouse model. Chronic PEA treatment was able to prevent cognitive impairment and preserve motivation. Moreover, PEA

protected hippocampal CA1 pyramidal neurons from spine density decrease in apical and basal dendrites. Neuroinflammatory astrogliosis was alleviated by PEA treatment by reducing GFAP levels in cortex and hippocampus. Furthermore, PEA prevented the transition of hippocampal microglial cells to a hyper-reactive phenotype, characterized by the extension and hyper-ramification of processes. Consistently, significant changes were observed in the hippocampal cytokine profile of PEA-treated Tg mice, exhibiting a reduction of cytokines responsible for recruiting immune system cells and triggering the neuroinflammatory response. PEA treatment was also able to modulate oxidative stress in Tg mice reducing significantly 3-nitrotyrosine levels in plasma, cortex and hippocampus, and reducing inducible nitric oxide synthase levels in cortex and hippocampus. These results demonstrate PEA neuroprotective and anti-inflammatory effects and its therapeutic potential in the early phases of AD pathology. PEA, as a modifier of the disease progression, might enhance the quality of life in the elderly and promote healthy ageing.

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Poster

PSTR013: Neural-Immune Signaling in Alzheimer’s Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.02/C20

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

Title: Semaglutide's cognitive rescue: insights from rat and mouse models of alzheimer's disease

Authors: E. ANDRIAMBELOSON, C. DUCHEMIN, B. HUYARD, F. LAUGA, L. PETER, E. POIRAUD, ***S. WAGNER**;
NEUROFIT, ILLKIRCH, France

Abstract: The ongoing clinical trials, Evoke and Evoke Plus, are investigating the potential benefits of Semaglutide (Ozempic), an anti-diabetic and anti-obesity medication, on various cognitive domains in individuals with early Alzheimer's disease. The herein study aims to assess the impact of Semaglutide treatment on a rat model of Alzheimer’s disease. Cognitive deficits were induced in the rats through an intracerebroventricular injection of amyloid-beta, reflecting the primary pathophysiological pathway associated with Alzheimer’s disease. Additionally, we evaluated Semaglutide's effect on LPS-induced cognitive deficits in mice and LPS-induced neuronal death in rat primary glia-neuron coculture to elucidate its impact, particularly regarding the involvement of its anti-inflammatory properties, in its beneficial effects against brain neuroinflammation. The intracerebroventricular injection of amyloid-beta in the rat was associated with a marked disruption of passive avoidance behavior after 2 weeks, indicating a memory retention deficit in these rats. This amyloid-beta-induced memory deficit was

significantly ameliorated by daily Semaglutide treatment compared to placebo. Furthermore, Semaglutide treatment significantly reduced the weight gain of amyloid-beta-treated rats, consistent with its anti-obesity effect. In mice, a single LPS injection induced a profound alternation deficit in the T-maze after 1 week, suggesting a cognitive deficit in these LPS-treated mice. Daily Semaglutide treatment significantly mitigated the cognitive deficit observed in LPS-treated mice compared to placebo, indicating its potential efficacy in combating neuroinflammation-associated cognitive impairments. This anti-inflammatory property of Semaglutide was further demonstrated by its ability to inhibit LPS-induced neuronal death in glia-neuron coculture system as well as its dose-response inhibition of associated nitric oxide production. These results support the beneficial effect of Semaglutide treatment against amyloid-beta-induced memory deficit and suggest an anti-inflammatory mechanism of action, highlighting its potential as a therapeutic option for Alzheimer's disease.

Disclosures: E. Andriambeloson: None. **C. Duchemin:** None. **B. Huyard:** None. **F. Lauga:** None. **L. Peter:** None. **E. Poiraud:** None. **S. Wagner:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.03/C21

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

Title: Investigating Sex Specific Hypothalamic Inflammation in Aging and Alzheimer's Disease

Authors: *E. ESFAHANI[1], A. SLIKE[2], P. MISHRA[2,3], A. ADLIMOGHADDAM[4], **B. C. ALBENSI**[5,3,6];
[1]St. Boniface Albrechtsen Res. Ctr., Winnipeg, MB, Canada; [2]Univ. of Manitoba, Winnipeg, MB, Canada; [3]St. Boniface Albrechtsen Research Centre, Winnipeg, MB, Canada; [4]Southern Illinois Univ., Chatham, IL; [5]Nova Southeastern Univ., Ft Lauderdale, FL; [6]University of Manitoba, Winnipeg, MB, Canada

Abstract: Introduction/Background: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory loss and cognitive decline, and two major pathological hallmarks: amyloid beta (Aβ) plaques and tau tangles. However, through the course of AD progression, we also observe an upregulation of inflammatory mediators and cytokines. Concurrently, recent findings highlight the potential involvement of inflammation in the pathogenesis of the AD along with sex-specific differences. Moreover, the presence of non-cognitive symptoms such as sleep-wake disorders and neuroendocrine alterations in AD patients, suggests the possibility of hypothalamic dysfunction. Hence, this leads us to investigate the role of the NF-κB mediated inflammation in the hypothalamus of both male and female 3xTg (AD transgenic mice). **Methods:** Hypothalami from male and female, 3xTg mice and C57BL/6 control mice were isolated and examined at 2 and 14 months of age. Pro-inflammatory markers (IL-1β, TNF-α, IL-6, IFN-γ) and anti-inflammatory markers (IL-10, IL-4) were measured in each

sample using enzyme-linked immunosorbent assay (ELISA). Changes in the levels of pro-inflammatory NF-κB subunits (p105/50, p65, and IκBα) were assessed via western blotting and ELISA. **Results:** We found a significant increase in the levels of pro-inflammatory cytokines IL-1β and TNF-α in 2-month and 14-month age groups in both male and female 3xTg and C57BL/6 mice. These results suggest a progressive inflammatory response in both strains over time. Additionally, the levels of anti-inflammatory cytokine IL-10 was found to be increased in 3xTg female mice compared to the C57BL/6 strain at 14-month age, suggestive of a potential compensatory mechanism in the 3xTg strain to respond to the increased neuroinflammation observed in AD. **Discussion:** Inflammation has emerged as a central mechanism in AD, and understanding the role of inflammatory mediators like NF-κB within the hypothalamus will shed light on the intricate mechanisms underlying non-cognitive symptoms of AD. Our study aims to gain deeper insight into the interplay between neuroinflammation and AD pathology. With this, we aim to contribute valuable insights to novel therapeutic strategies targeting hypothalamic dysfunction in AD.

Disclosures: E. Esfahani: None. **A. Slike:** None. **P. Mishra:** None. **A. Adlimoghaddam:** None. **B.C. Albensi:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.04/C22

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

Support: OSU Presidential Fellowship
R03 AG067061
R21 AG071133
OSU Psychiatry Seed Grant

Title: The influence of TLR4 mediated neuroinflammation and the complement system on HFD-evoked memory and synaptic impairments in an AD mouse model

Authors: *S. MACKEY-ALFONSO[1], J. BLACKWELL[1], M. BUTLER[1], A. DEL AGUILA[1], L. M. PYTER[1], R. M. BARRIENTOS[2];
[2]Inst. for Behavioral Med. Res., [1]The Ohio State Univ., Columbus, OH

Abstract: Alzheimer's Disease (AD) is a neurodegenerative disease characterized by profound memory impairments, synaptic loss, TLR4-mediated neuroinflammation, and hallmark pathologies. High-fat diet (HFD) consumption increases risk of developing AD even after controlling for metabolic syndrome, pointing to a role of the diet itself in AD vulnerability. We previously demonstrated a short-term HFD regimen, which does not cause metabolic syndrome, exacerbated memory impairments, neuroinflammation, and evoked synaptic dysregulation in 3xTg-AD mice. We also showed synapses isolated from HFD-fed AD mice were phagocytosed,

in vitro, more readily by a microglial cell line and was ameliorated with a complement receptor inhibitor, neutrophil inhibitory factor (NIF). The complement system, which normally only tags redundant or damaged synapses for pruning, can become pathologically overactivated by neuroinflammation leading to degradation of healthy synapses. These data pointed to complement as a potential mechanistic culprit underlying the observed memory deficits. We hypothesize HFD-evoked neuroinflammation over activates the complement system, degrading synapses and hence worsening memory. To test this mechanism *in vivo*, at the time of consumption of either chow or HFD, 3xTg-AD mice were injected intra-cisterna magna with either vehicle or a TLR4 inhibitor (LPS-rs Ultrapure). We examined the expression of complement proteins and synaptic markers in the hippocampus. In a separate cohort of mice, vehicle, NIF, or LPS-rs were injected. Brains were collected for *ex vivo* analysis of synaptic phagocytosis via flow cytometry. Preliminary data suggests LPS-rs reduces complement deposition and increases synaptic density markers. Early findings indicate that NIF reduces synaptic phagocytosis in the AD+HFD group which we expect will rescue memory deficits in this group. These data will help us validate our *in vitro* findings and untangle the influence of the complement system versus neuroinflammation on HFD-evoked precipitous memory decline in an AD mouse model. These data provide clues in understanding HFD-mediated AD vulnerability.

Disclosures: S. Mackey-Alfonso: None. **J. Blackwell:** None. **M. Butler:** None. **A. del Aguila:** None. **L.M. Pyter:** None. **R.M. Barrientos:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.05/C23

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

Support: 2021/43/B/NZ4/01133 National Science Centre, Poland (Task 1 and 5).

Title: Formyl peptide receptor 2 as a target for limitation of prolonged neuroinflammation: link to Alzheimer's pathology

Authors: *A. BASTA-KAIM[1], J. FRYDRYCH[2], E. TROJAN[2], E. LACIVITA[3];
[1]Dept of Exptl. Neuroendocrinology, [2]Exptl. Neuroendocrinology, Maj Inst. of Pharmacol. Polish Acad. of Sci., Krakow, Poland; [3]Dept. of Pharmacy, Drug Sci. Univ. of Bari, Bari, Italy

Abstract: The most common form of pathologically accelerated cognitive decay is the one observed in Alzheimer's disease (AD). The hallmarks of AD include extracellular plaques containing amyloid beta (Aβ) and intracellular neurofibrillary tangles (NFT). Furthermore, prolonged neuroinflammation plays a pivotal role in the pathogenesis of AD. Short-term inflammatory response enables the repair and restoration of homeostasis, whereas disturbances in the resolution of inflammation (RoI) lead to chronic inflammation. RoI is regulated by

specialized pro-resolving mediators (SPMs), which exert their biological effects through interactions with formyl peptide receptor 2 (FPR2), a "promiscuous" receptor that can mediate anti-inflammatory and pro-inflammatory effects depending on the ligand structure and biodistribution. Supporting RoI through new FPR2 ligands could allow for better RoI processes in the brain related to AD pathology. In this study, we aim to determine the age-dependent changes in the levels of FPR2, AnxA1, LXA4, and Aβ42/Aβ40 ratio in the frontal cortex and hippocampus in C57BL/6J (WT) and in $APP^{NL-F/NL-F}$ knock-in mice (KI), which expressed humanized late onset model of Alzheimer disease (LOAD). Next, we assessed the pro-resolving effect of novel ureidopropanamide FPR2 ligands (Fz6, AMS21) to demonstrate their potential to support RoI. For these studies, we used microglial cells isolated from ageing mice using the BeadsMACS Separator, treated next post-in vivo with new FPR2 agonists. We show that the levels of FPR2 were higher only in the hippocampus of 9- and 12-month-old KI mice. The ratio of Aβ42/Aβ40 elevated in the hippocampus and frontal cortex of 9- and 12-month-old KI mice in comparison to age-matched WT animals. Levels of both measured anti-inflammatory FPR2 agonists - LXA4 and ANXA1 were lower in the hippocampus of KI mice at any age. We have also shown that the new agonists inhibit the inflammatory response and exert pro-resolving activity. Our study proves that RoI disturbances have been determined by age, genetic background, and brain structure. Moreover, we observed the limitation of the availability of pro-resolving FPR2 ligands and an increase in Aβ-mediated inflammatory FPR2 overactivation. Together, these findings identify FPR2 as a promising target for therapeutic intervention. We propose that new exogenous pro-resolving FPR2 ligands could attenuate endogenous RoI deficits and, in this way, limit the impact of chronic inflammatory processes on the pathology of Alzheimer's disease. Supported by the grant no. 2021/43/B/NZ4/01133, National Science Centre, Poland (Task 1 and 5).

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Poster

PSTR013: Neural-Immune Signaling in Alzheimer’s Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.06/C24

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

Support: AG062469 to SSM
AG062135 to MKL
NS108686 to MKL

Title: Loss of glyoxalase-1 enhances neuroinflammation and neurodegeneration independent from Aβ pathology in $APP_{SWE}/PS1_{\Delta E9}$ mouse model of Alzheimer’s disease

Authors: *A. O. IMAM-FULANI[1], S. RAO[2], S. PHILLIP[1], K. CHENNAVAJULA[1], J. MEINTS[1], S. S. MORE[2], M. K. LEE[1,3];
[1]Dept. of Neuroscience, Univ. of Minnesota, Minneapolis, MN; [2]Ctr. for Drug Design, Col. of

Pharmacy, Univ. of Minnesota, Minneapolis, MN; [3]Inst. for Translational Neuroscience, Univ. of Minnesota, Minneapolis, MN

Abstract: Alzheimer's disease (AD) is characterized by Aβ deposits, neurodegeneration, and oxidative stress. We previously showed that supplementation of the $APP_{SWE}/PS1_{\Delta E9}$ (APP/PS1) model of cerebral amyloid pathology with novel GSH analog attenuates oxidative stress and AD-related pathology (PMC8614797). We propose that the therapeutic effect of the GSH analog is partly due to the restoration of compromised glyoxalase 1 (Glo1) activity in the AD mouse brain, increasing reduced oxidized sugars (methylglyoxal, MG) that promote oxidative stress and inflammation. To determine the role of Glo1 in AD, we generated APP/PS1 mice lacking one ($Glo1^{Het}$) or both ($Glo1^{KO}$) copies of the Glo1 gene and analyzed them at 12 months of age. Biochemical and Western blot analysis revealed a significant increase in the levels of MG and advanced glycation end-products (AGE) in APP/PS mice lacking Glo1. Surprisingly, the constitutive loss of Glo1 did not exacerbate Aβ pathology in APP/PS1 mice, while partial loss of Glo1 activity in $AP/Glo1^{Het}$ led to a significant increase in overall Aβ pathology. The results indicate a developmental compensatory response to the complete loss of Glo1 expression. Indeed, the biochemical analysis showed significantly increased GSH levels in $APP/PS1/Glo1^{KO}$, suggesting that the GSH biosynthesis might be linked to Aβ pathology. Because MG and AGE are associated with increased inflammation, we also examined if microglial activation correlated with MG/AGE levels or Aβ pathology. Activated microglia were selectively analyzed by immunostaining for CD68. As expected, increased Aβ pathology in $APP/PS1/Glo1^{Het}$ mice was associated with increased CD68 staining. Despite the reduced Aβ pathology in the $APP/PS1/Glo1^{KO}$ mice, the level of CD68 staining was much higher than in the $APP/PS1/Glo1^{WT}$ mice. Analysis of TH+ afferents in the cortex and hippocampus, arising mostly from Locus Coeruleus (LC), showed a greater loss of TH+ afferents in Glo1 deficient APP/PS1 mice, independent of the extent of Aβ pathology. Finally, we examined the integrity of TH+ neurons in the LC. The $APP/PS1/Glo1^{WT}$ mice showed a modest, non-significant reduction in the total TH+ neurons relative to age-matched controls. However, the loss of TH+ neurons in LC was significant in the APP/PS1 lacking Glo1 expression, irrespective of the Aβ pathology. Our results show that Glo1 function is important for modulating neuroinflammation resulting from MG/AGE formation and subsequent neurodegeneration. Further, increased neuroinflammation, rather than Aβ pathology, correlates with progressive neurodegeneration in APP/PS1 model.

Disclosures: A.O. Imam-Fulani: None. **S. Rao:** None. **S. Phillip:** None. **K. Chennavajula:** None. **J. Meints:** None. **S.S. More:** None. **M.K. Lee:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.07/C25

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

Support: 451-03-66/2024-03/200007
23CDA1051814
24IVPHA1288043

Title: The Effects of Alfaxalone on Amyloid Pathology in the Brain of Male and Female Humanized APP Mice

Authors: M. PEROVIC[1], N. MILOVANOVIC[1], D. PAVLOVIC[2], Z. PALMER[2], J. CIRIC[1], *V. TESIC[2];
[1]IBISS, Belgrade, Serbia; [2]LSU Hlth. Sci. Ctr., Shreveport, LA

Abstract: Alzheimer's disease (AD) is a progressive age-associated brain disorder and the leading cause of dementia and disability in the elderly worldwide. Naturally occurring neurosteroid, allopregnanolone, was demonstrated to exert numerous neuroprotective effects and reduce AD pathology burden by decreasing amyloid-beta deposition and consequent neuroinflammation and neurodegeneration leading to the amelioration of cognitive and behavioral deficits in AD models.It has also been shown that the use of naturally occurring neurosteroids, including allopregnanolone, can disturb hormonal balance in the brain. Alfaxalone (ALX), a synthetic neurosteroid analog of allopregnanolone is devoid of endocrine hormonal activity. In the present study, the effects of ALX treatment on AD pathology markers were examined in the APP-NL-G-F knock-in (KI) mouse model of AD. The 9-month-old male and female KI mice and their non-KI littermates (wild-type, WT) were treated with a dose of ALX (40 mg/kg; s.c., 1/w) for four weeks, and the effects on key histopathological markers, amyloid plaques, and consequent gliosis were examined in brain regions important for learning and memory by immunostaining and quantitative analysis. Glial acidic protein (GFAP) was used as a marker for astrocytes, while ionized calcium-binding adapter molecule type 1 (Iba-1) was used for labeling microglial cells. Morphological analysis of plaque number and average size was accompanied by the full characterization of gliosis performed by quantitative analysis of the relative intensity of fluorescence signal for GFAP and Iba-1 expression. Our findings reveal profound differences in the effects of an anesthetic dose of ALX on AD-like amyloidosis in male and female APP-NL-G-F mice and are thus in line with well-established sex-biased differences in prevalence, progression rate and severity of AD in humans further establishing sex as a crucial variable in disease heterogeneity.

Disclosures: M. Perovic: None. **N. Milovanovic:** None. **D. Pavlovic:** None. **Z. Palmer:** None. **J. Ciric:** None. **V. Tesic:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.08/C26

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

Title: Neuropathology development of Alzheimer's disease features in female 3xTg mice linked to neuroinflammation

Authors: *P. P. MARTINEZ CUEVAS[1], J. LUNA[2], Z. KOLAHCHI[3], M. A. RAMIREZ-LEE, Sr.[4], S. JIMENEZ[1], E. CUEVAS[5];
[1]Neurol., Univ. of Texas Med. Br., Galveston, TX; [2]Dept. de investigacion, innovacion y posgrado, Univ. Politecnica de Pachuca, Zempoala, Mexico; [3]Neurol., university of Texas medical branch (UTMB), Galveston, TX; [4]Neurotoxicology, Natl. Ctr. For Toxicological Res., SLP, Mexico; [5]NEUROLOGY, UTMB, Galveston, TX

Abstract: Neuropathology development of Alzheimer's disease features in female 3xTg mice linked to neuroinflammation. [1]Pedro Martinez, [2-4]Jose Luna-Muñoz, [1]Zahra Kolahchi, [5]Alejandro Ramirez Lee. [1]Elvis Cuevas
[1]Department of Neurology, Mitchell Center for Neurodegenerative Diseases, University of Texas Medical Branch, Galveston, TX, USA.[2]National Dementia Biobank. AMPAEYDEN A.C., Federación Mexicana de Alzheimer; FEDMA A.C. México.[3]Director of Research, Innovation and Postgraduate. Universidad Politécnica de Pachuca. Zempoala; México. [4]National Brain Bank-UNPHU, Universidad Nacional Pedro Henríquez Ureña, Dominican Republic. [5]Cook Research Incorporated, West Lafayette, IN, USA
The female 3xTg-AD model is a valuable tool for investigating pathogenic mechanisms and potential therapeutic interventions since this model mimics the main pathological features of AD. Neuroinflammation is considered a main pathological factor that contributes significantly to AD development. It has been suggested that the increased risk of AD in women is because women have a diminished capability to regulate the neuroinflammation that is characteristic of AD. However, there is no clear evidence of whether neuroinflammation contributes to the development of AD pathology in females. Therefore, we tested neuropathology (amyloid-beta isoforms, APP, Tau isoforms, and GFAP and IBA1) changes in 3xTg-AD female and wild-type (WT) mice at 3-, 6-, 9- and 12-months of age by immunohistochemistry analysis. We found that 3xTg-AD females displayed significant neuropathological changes associated with neuroinflammation markers, compared to WT females, especially at 9 months. This work supports the hypothesis that the development and progression of neuropathological hallmarks of AD may be linked to neuroinflammation. This knowledge highlights the role of neuroinflammation in the onset of AD. Therefore, it would improve the development of new drugs intended to treat or slow AD progression in women.**Acknowledgments:** We thank NCTR for the use of the tissue, we also thank Susan Burks, Bonnie Robinson, and John Talpos for making the brain mice tissue available. **Funds:** Startup package of NVRCL and EC.**Keywords:** Alzheimer's disease, female 3xTg, neuroinflammation, amyloid-beta, Tau.

Disclosures: P.P. Martinez Cuevas: None. **J. Luna:** None. **Z. Kolahchi:** None. **M.A. Ramirez-Lee:** None. **S. Jimenez:** None. **E. Cuevas:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.09/C27

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

Title: Pharmacological enhancement of cholinergic neurotransmission alleviates neuroinflammation and improves functional outcomes in a triple transgenic mouse model of Alzheimer’s disease

Authors: *G. DI BENEDETTO, A. MUNAFO', A. CANTONE, S. A. TORRISI, C. BURGALETTO, C. BELLANCA, G. GAUDIO, G. LEGGIO, R. BERNARDINI, G. CANTARELLA;
Dept. of Biomed. and Biotechnological Sci., Univ. of Catania, Catania, Italy

Abstract: Alzheimer’s disease (AD) is the most common neurodegenerative disorder affecting the elderly population worldwide. Due to the multifactorial nature of the disease, involving impairment of cholinergic neurotransmission and immune system, previous attempts to find effective treatments have faced challenges. In such scenario, we attempted to investigate the effects of alpha- glyceryl-phosphoryl-choline (α-GPC), a cholinomimetic molecule, on neuroinflammation and memory outcome in the triple transgenic mouse model of AD (3xTg-AD). Mice were enrolled at 4 months of age, treated orally with α-GPC dissolved in drinking water at a concentration resulting in an average daily dose of 100 mg/kg for 8 months and sacrificed at 12 months of age. Thereafter, inflammatory markers, as well as cognitive parameters, were measured. Chronic α-GPC treatment reduced accumulation of amyloid deposits and led to a substantial re-balance of the inflammatory response of resident innate immune cells, astrocytes and microglia. Specifically, fluorescent immunohistochemistry and Western blot analysis showed that α-GPC contributed to reduction of cortical and hippocampal reactive astrocytes and pro-inflammatory microglia, concurrently increasing the expression of anti-inflammatory molecules. Whereas α-GPC beneficially affect the synaptic marker synaptophysin in the hippocampus. Furthermore, we observed that α- GPC was effective in restoring cognitive dysfunction, as measured by the Novel Object Recognition test, wherein 3xTg-AD mice treated with α-GPC significantly spent more time exploring the novel object compared to 3xTg-AD untreated mice. In conclusion, chronic treatment with α-GPC exhibited a significant anti-inflammatory activity and sustained the key function of hippocampal synapses, crucial for the maintenance of a regular cognitive status. In light of our results, we suggest that α-GPC could be exploited as a promising therapeutic approach in early phases of AD.

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Poster

PSTR013: Neural-Immune Signaling in Alzheimer’s Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.10/C28

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

Support: Progetti di Rilevante Interesse Nazionale" (PRIN) 2017 2017YH3SXK

Title: Evaluating the effect of immune activation in the 3xTg mouse model of Alzheimer's disease.

Authors: *R. MOSTALLINO[1], A. MASTIO[1], M. SANTONI[1], C. SAGHEDDU[1], M. C. MOSTALLINO[2], F. SANNA[1], M. PISTIS[1,3,4], M. CASTELLI[1];
[1]Dept. of Biomed. Sci., Univ. of Cagliari, Monserrato, Italy; [2]Natl. Res. Council, CNR, Monserrato, Italy; [3]Section of Cagliari, Neurosci. Inst. Natl. Res. Council of Italy (CNR), Cagliari, Italy; [4]Unit of Clin. Pharmacology, Univ. Hosp., Cagliari, Italy

Abstract: Alzheimer's Disease (AD) is the most prevalent form of dementia characterized by chronic and progressive neurodegeneration resulting in cognitive impairment, memory loss, and behavioral alteration. Despite growing evidence suggesting the relationship between neuroinflammation and AD neuropathology, the role of systemic inflammation and brain abnormalities and their relationship in the onset and progression of AD is still a matter of debate. Here, we tested the hypothesis that an inflammatory insult might worsen disease progression in a validated mouse model of AD.Female 4-months-old 3xTg-AD mice (APPswe, Tau_{P301L} and $PS1_{M146V}^{+/-}$) received a single intraperitoneal injection of polyriboinosinic-polyribocytidylic acid (Poly (I:C)), a synthetic double-stranded RNA that triggers an innate immune response. At 6 and 15 months of age, we performed immunological, biochemical, and staining analysis in the hippocampus, and *in vivo* extracellular single-unit recordings in anesthetized mice in the mPFC.We found increased levels of pro-inflammatory cytokines and chemokines in Poly (I:C)-treated mice at both ages. Specifically, 6-month-old mice treated with Poly (I:C) showed increased expression of hippocampal Interleukin (IL)-1α, IL-1β, IL-2, IL-5, IL-9, and regulated on activation normal T-cells expressed and secreted (RANTES) compared to control mice. IL-1β and IL-5 levels remained upregulated in Poly (I:C)-treated 15-month-old 3xTg-AD mice, which also showed increased levels of chemokines Eotaxin and monocyte chemoattractant protein 1 (MCP-1). Conversely, amyloid precursor protein and its proteolytic fragments, as well as Tau protein and different phosphorylated forms, were similar in 15-month-old vehicle- and Poly (I:C)-treated animals. Finally, 15-month-old mice treated with Poly (I:C) showed decreased total spine density of the apical dendritic branches of CA1 pyramidal neurons, with no differences in the basal branches. Putative mPFC pyramidal neurons from Poly (I:C)-treated mice showed no differences in firing rate compared to the vehicle-treated group. Furthermore, no differences were observed in the firing
activity, as determined by the number of spontaneously activated neurons, or the firing pattern, as measured by the coefficient of variation.Taken together these results suggest that: i) Poly (I:C) might represent an interesting tool to investigate neuroinflammation and its involvement in the neurodegeneration of AD pathology and ii) the immune activation in this mouse model of AD induces a long-lasting neuroinflammatory state and leads to synaptic damage that could result in a detrimental progression of the pathology.

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Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.11/C29

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

Support: NIH 1RF1AG069378-01
UND School of Medicine and Health Sciences

Title: Examining microbial components, lipopolysaccharide and peptidoglycan, in human Alzheimer's disease and App^{NL-G-F} mouse model brains

Authors: *A. M. FLODEN, C. K. COMBS;
Biomed. Sci., Univ. of North Dakota, Grand Forks, ND

Abstract: Alzheimer's disease (AD) hallmark histologic changes include amyloid beta (Aβ) plaques and neurofibrillary tangles. In addition, microgliosis, astrogliosis, and immune changes are observed in diseased brains. Although Aβ peptides are often hypothesized as stimulating ligands for reactive gliosis and brain inflammatory change during disease, heterogeneous stimuli are likely. For example, several reports have identified bacterial cell wall components such as lipopolysaccharide (LPS) in both human AD brains as well as its mouse models. Moreover, numerous studies have shown increasing relevance of the contribution of the gut and oral microbiome to AD disease processes. To test whether the bacterial cell wall components, LPS and peptidoglycan, accumulate in AD brains as potential drivers of inflammatory change, we performed ELISAs to quantify their levels from the mid-temporal gyrus (MTG) of eight male and female AD and age-matched controls. LPS and peptidoglycan ELISA results from the human brains were compared to ELISAs from 6-month-old littermate control C57BL/6 wild type and *App* $^{NL-G-F}$ mouse parietal cortices. Surprisingly, we did not observe a significant difference in LPS levels comparing control to AD brains in either sex. However, both male and female AD brains had elevated peptidoglycan levels compared to their respective control brains. When we compared the parietal cortex of the AD mouse model, *App* ^{NLGF}, to their littermate controls, there were no significant differences in either LPS or peptidoglycan levels for either sex. These data support the increasing recognition that bacterial components may serve as activating ligands in the AD brain to influence inflammatory conditions. In addition, our findings suggest that peptidoglycan may be an interesting ligand for future studies of relevance to AD. Finally, future work comparing alternative brain regions, ages, or animal models is needed to accurately model human changes in the mouse models.

Disclosures: A.M. Floden: None. **C.K. Combs:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.12/C30

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

Support: R35 NS116835
R01 FD00747
RG-1907-34532,
T32 NS121727

Title: Assessing the subacute impact of coronavirus-induced neuroinflammation on amyloid-beta pathology in 5XFAD mice

Authors: *D. I. JAVONILLO, T. E. LANE;
Neurobio. AND BEHAVIOR, Univ. of California, Irvine, Irvine, CA

Abstract: Alzheimer’s Disease (AD) is a progressive neurodegenerative disease characterized by the aggregation of extracellular amyloid-beta (Aβ) plaques, neurofibrillary tangles containing hyperphosphorylated tau protein, and chronic neuroinflammation. Recent studies revealed key immunological mechanisms within the central nervous system (CNS) that contribute to AD pathology. Additionally, epidemiological and post-mortem analysis of AD human brains have also associated viral encephalitis exposure (i.e., viral-induced neuroinflammation) with the development of AD pathology, highlighting the need to better understand how viral encephalitis and neuroimmune mechanisms within the brain may impact AD pathologies such as Aβ plaque deposition. Using the neurotropic JHM strain of murine coronavirus, we previously reported the robust inflammatory responses to infection orchestrating sustained infiltration of peripheral immune cells (i.e. monocyte/macrophages and T cells) within the CNS. To determine the extent to which coronavirus-induced encephalitis impacts established Aβ plaque deposition, we intracranially infected 5xFAD mice with the neurotropic JHM coronavirus. Histological staining of Aβ plaques revealed reduced plaque volumes in the subiculum region of JHMV-infected 5xFAD mice at 12 days post-infection. Additionally, a reduced density of Aβ plaques was found within the somatosensory cortex of JHMV-infected mice. Bulk RNA sequencing of uninfected and JHMV-infected 5xFAD brain homogenates identified upregulated DEGs and pathways associated with anti-viral immune and inflammatory responses. Both flow cytometry and immunohistological staining for galectin-3/MAC2 demonstrate robust peripheral monocyte/macrophage infiltration into the brains of JHMV-infected 5xFAD mice, in addition to $CD4^+$ and $CD8^+$ T cell infiltration. Confocal analysis revealed significantly higher $MAC2^+$ cell infiltration in JHMV-infected 5xFAD brains compared to uninfected controls. Brain regions with higher infiltration of $MAC2^+$ cells demonstrated a significant correlation with reduced Aβ plaque volumes. Together, these findings suggest relevant interactions involving infiltrating monocytes/macrophages to reduce Aβ plaque burden in 5xFAD mice during subacute JHMV infection. Future experiments aim to further dissect inflammatory mechanisms between peripheral monocytes/macrophages and Aβ pathology. Data derived from these experiments will further elucidate the viral-induced neuroimmune mechanisms that affect AD pathology and offer an opportunity to determine how these neuropathologic changes such as subsequent neuronal damage occur.

Disclosures: **D.I. Javonillo:** None. **T.E. Lane:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

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Program #/Poster #: PSTR013.13/C31

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

Support: NIA grant # R01AG055545
NIA grant # R56AG077814
R21AG079550

Title: The Effect of a Pathogen-rich environment on the development of Tauopathy in PS19 mice

Authors: *M. KANTOROVICH, D. SHAPIRO, M. HASAN, J. PACIA, L. BEURA, G. VALDEZ;
Brown Univ., Providence, RI

Abstract: Alzheimer's Disease (AD) is an irreversible, progressive dementia which presents with neurodegeneration, synaptic loss, and neuroinflammation. While humans are constantly exposed to pathogens in daily life, experimental mice raised in specific pathogen free (SPF) conditions have comparably immature immune systems. Given that significant changes in immune cells and function have been noted in AD pathology, the lack of immune maturity in SPF mice presents limitations in effectively modeling AD processes, including in the development of tauopathy. To address this potential shortcoming, this study was designed to compare several core aspects of AD-related tauopathy in PS19 mice, a model of tauopathy, housed in clean versus "dirty" conditions. Mice housed in "dirty" conditions are purposefully exposed to a variety of pathogens to constantly challenge their immune system. Flow cytometry experiments have revealed a higher level of immune system maturity in dirty compared to clean PS19 mice. This includes dirty PS19 mice presenting with higher levels of terminally differentiated and antigen experienced T-cells than clean PS19 mice. Histopathological analysis of the PS19 brains provides important clues about the effect of a dirty environment on the onset and progression of AD-related tauopathy on neurons and glial cells. Thus, our initial data suggest that studying the PS19 mice in dirty conditions may be needed to generate additional and critical leads to mitigate tauopathy-induced neurodegeneration.

Disclosures: **M. Kantorovich:** None. **D. Shapiro:** None. **M. Hasan:** None. **J. Pacia:** None. **L. Beura:** None. **G. Valdez:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.14/C32

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

Support: European Union
Region Grand Est
France 2030

Title: Towards new relevant neuroinflammation models using oligomers involved in Alzheimer’s disease for target validation and drug testing

Authors: *N. VIOLLE, A. ALLOUCHE, M. BALDONI, L. MAGADOUX, L. DIER, J. COLIN;
ETAP-Lab, Vandoeuvre-lès-Nancy, France

Abstract: To date soluble oligomeric species and neuroinflammation are core targets of Alzheimer's disease (AD), interacting in an intimate detrimental dialogue. Microglia and astrocytes are major key regulators of inflammatory responses in the central nervous system. In AD, amyloid-beta oligomers (AβO) and tau oligomers (TauO) induce unbalanced activation of microglia and astrocytes, which instigates exaggerated inflammatory responses, called neuroinflammation, and can directly damage neurons and disrupt neuronal function. Relevant in vitro and in vivo models for targeting and/or preventing neuroinflammation induced by oligomer are needed to assess new therapeutic strategies for AD.
Here, we report the progress in our development of novel neuroinflammation models of AD, focusing on activated glial cells (i.e. microglia and astrocytes) by low quantities of AβO and TauO prepared inhouse. These preparations are well-characterized by various methods (SDS-page, dot-blot, 8-Anilino-1-NaphthaleneSulfonic acid (ANS) and Sedimentation Velocity Analytical Ultracentrifugation (SV-AUC) assays). Assessment of phenotype changes in astrocytes derived from human-induced pluripotent stem cells (hiPSCs) were performed using a high content imaging system. Then, both astrocytes and microglia activations were evaluated after an intracerebral microinjection of oligomers in C57Bl6J wild-type mice.
In vitro, oligomers induced reproducible and robust changes in human astrocytes, characterized by a typical transition to polygonal morphology and a shift to an inflammatory phenotype with secretion of inflammatory cytokines and changes in protein expression profiles. In vivo, an intracerebral microinjection of either AβO or TauO in C57Bl6J mice, led to a cerebral inflammation and promoted functional alteration of astrocytes and microglia in different brain regions. Indeed, these preparations induced exacerbated microglial and astrocytic reactivity associated with elevated pro-inflammatory cytokine secretion.
In conclusion, we characterized new experimental situations to better understand the neuroinflammatory mechanisms underlying AD, an essential step before developing effective therapies.

Disclosures: N. Violle: A. Employment/Salary (full or part-time):; ETAP-Lab. **A. Allouche:** A. Employment/Salary (full or part-time):; ETAP-Lab. **M. Baldoni:** A. Employment/Salary (full or part-time):; ETAP-Lab. **L. Magadoux:** A. Employment/Salary (full or part-time):; ETAP-Lab.

L. Dier: A. Employment/Salary (full or part-time):; ETAP-Lab. **J. Colin:** A. Employment/Salary (full or part-time):; ETAP-Lab.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.15/C33

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

Support: IUFW Research & Scholarly Activity Grant

Title: Transient cerebral ischemia exacerbates amyloid beta-driven neuropathology and cognitive decline in the human APP knock-in mouse model of Alzheimer's disease.

Authors: *H. HUANG[1], P.-C. KUO[2], H. PARAISO[3], B. SCOFIELD[2], J. YEN[2], I.-C. I. YU[3,4]; [1]Biol. Sci., Purdue Univ. Fort Wayne, Fort Wayne, IN; [2]Microbiology & Immunol., Indiana Univ. Sch. of Med., Fort Wayne, IN; [3]Anatomy, Cell Biol. & Physiol., Indiana Univ. Sch. of Med., Fort Wayne, IN; [4]Stark Neuroscience Research Institute, Indianapolis, IN

Abstract: Alzheimer's disease (AD) is a chronic neurodegenerative condition primarily characterized by the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles. Notably, up to 80% of AD patients display significant vascular abnormalities at autopsy, indicating a blend of cerebrovascular disease and AD pathophysiology. Cerebral ischemia is known to lead to a range of vascular complications, including cortical infarctions, white matter lesions, and microbleeds, which may exacerbate neurodegeneration and dementia in AD patients following strokes. This study investigated the interactions between cerebral ischemia and Aβ-associated neuropathology using App^{SAA} knock-in mice. These mice express a humanized $Aβ_{1-42}$ sequence containing Swedish (KM670/671NL), Arctic (E693G), and Austrian (T714I) mutations. We induced unilateral transient ischemia by occluding the right middle cerebral artery (tMCAO) for 20 minutes. Three months post-ischemia, we assessed Aβ deposits in the brain using anti-$Aβ_{1-16}$ antibody (6E10) and methoxy-X04 staining. Our analysis revealed no significant difference in Aβ plaque accumulation between the ischemic and non-ischemic hemispheres. However, a distinction in plaque morphology was noted, with an increase in filamentous Aβ plaques in the ischemic hemisphere as determined by differentiating compact versus filamentous plaques using X04 versus 6E10 staining. These findings indicate that ischemia may influence the characteristics of Aβ deposits in the ischemic brains of App^{SAA} mice. Subsequent behavioral assessments, including the open-field test for locomotor activity and the accelerating rotarod assay for motor skill learning, initially showed no significant differences in motor activities between tMCAO and sham control groups. However, tMCAO App^{SAA} mice displayed a substantial decline in motor performance over six training sessions, suggesting an impaired ability in motor skill learning. The novel object recognition test also confirmed recognition memory deficits, indicating impaired functions in learning and memory. Together, these results highlighted the role of cerebral ischemia and subsequent vascular pathology in

exacerbating the progression of AD and the importance of protecting the brain from ischemic insults in managing AD.

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Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.16/C34

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

Support: NIH/NIA RF1 AG060057 (CAL)
Philanthropy

Title: Deciphering the role of complement C3 in anti-amyloid antibody-induced ARIA

Authors: *M.-T. PAPAVERGI[1,2], T. BARBOUR[3], T. SAIDO[4], D. J. EYERMAN[3], C. A. LEMERE[1];
[1]Neurol., Brigham & Women's Hospital; Harvard Med. Sch., BOSTON, MA; [2]Psychiatry and Neuropsychology, Sch. for Mental Hlth. and Neurosci. (MHeNs), Maastricht, Netherlands; [3]Apellis Pharmaceuticals, Waltham, MA; [4]RIKEN Brain Sci. Inst., Wako, Japan

Abstract: The complement cascade is an arm of innate immunity that protects against pathogens. C3 is the molecule at which multiple complement signaling pathways converge and has emerged as a key player in Alzheimer's disease (AD). AD currently afflicts an estimate of 6.9 million Americans (www.alz.org) and is designated a global public health priority by the World Health Organization. Plaque-binding anti-amyloid-β antibodies (anti-Aβ) have been shown to trigger vasogenic edema and hemorrhages, known as Amyloid-Related Imaging Abnormalities (ARIA-E and ARIA-H) in a subset of patients in AD clinical trials. Under ischemic conditions, elevated C3d (C3 fragment) levels lead to the conversion of astrocytes into a pro-inflammatory A1 phenotype, exacerbating vascular inflammation, edema, and hemorrhage. We asked whether global C3 lowering protects against anti-Aβ-induced microhemorrhages in mice. To this end, we crossed our $C3^{fl/fl;Rosa26CreERT2}$ mice to $APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice (APP;C3iKO) to globally lower C3 in adult amyloid mice. Eighteen-month-old mice were injected intraperitoneally (i.p.) with either tamoxifen (TAM) or corn oil (CO, control) (n = 10/group; 5F, 5M) for 5 consecutive days. After 3 weeks, all mice received weekly i.p. injections of 25 mg/kg 3D6-L anti-Aβ mAb, a murine analog of bapineuzumab known to cause microhemorrhages, for 7 weeks. APP;C3iKO mice that did not receive either TAM/CO or 3D6-L mAb (n = 5F, 4M) were also included. All mice were euthanized at 20 months of age. C3 serum levels were significantly reduced by 65-70% following TAM treatment, indicating successful C3 knockdown. There were no significant sex differences in C3 serum levels, nevertheless female mice had higher C3 serum levels than males in all groups. Previously, we observed that the cerebellum is the brain region

most susceptible to anti-Aβ-induced microhemorrhages in several APP mouse models. Here, hemosiderin staining indicated that microhemorrhages were more prominent in the cerebellum of CO-treated mice following anti-Aβ treatment compared to TAM-treated mice. C3 levels were significantly correlated with microhemorrhages in the TAM-treated mice, i.e. lower C3 correlated with fewer microhemorrhages, while this correlation was not significant for the CO-treated group. No significant sex differences were detected regarding microhemorrhages. Our results suggest that C3 lowering might protect against anti-amyloid-induced microhemorrhages. Additional analyses are underway to identify mechanisms underlying this process and the potential of C3 as a therapeutical target for AD.

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Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.17/C35

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

Support: Cure Alzheimer's Fund

Title: The complement system may regulate hippocampal plasticity and influence cognition by sex and APOE genotype

Authors: *X. LIN[1], K. GO[3], J. E. RICHARD[5,4], P. A. SHEPPARD[6], N. W.-L. DIEKOW[7], L. A. GALEA[3,2];
[1]Inst. of Med. Sci., Univ. of Toronto, TORONTO, ON, Canada; [2]Univ. of Toronto, Toronto, ON, Canada; [3]Ctr. for Addiction and Mental Hlth., TORONTO, ON, Canada; [4]Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada; [5]Univ. of Gothenburg, Goeteborg, Sweden; [6]Robarts Res. Inst., Western Univ., London, ON, Canada; [7]King's Col. London, Hamburg, Germany

Abstract: Title: Complement System Regulates Hippocampal Plasticity and Influences Cognition by Sex and APOE Genotype
Authors: Xinyi Lin, Kimberly A Go, Jennifer E Richard, Paul AS Sheppard, Natascha Diekow, Liisa AM Galea
Abstract: Females with Alzheimer's disease (AD) have more severe cognitive decline and pathological changes in the brain, accompanied by faster hippocampal atrophy, greater AD

neuropathology and steeper cognitive decline than males with AD. Notably, female APOEε4 carriers have a higher risk of developing AD earlier and exhibit greater cognitive decline than male APOEε4 carriers at middle age. Neuroinflammation is disrupted in AD. The activation of phagocytic complement signals, such as C3, on microglia causes chronic inflammation and triggers phagocytosis in AD. Inhibition or knockdown of C3 can reduce AD neuropathology in AD animal models. Although complement genes are found to exhibit sex differences in rodents and humans, their roles in cognition by sex and APOE genotype remain unexplored. As such, the present research aims to determine whether sex differences in cognition are differentially exacerbated by APOEε4 genotype and mediated by neuroinflammation.
We used 6-month-old male and female humanized (h) APOEε3 and hAPOEε4 adult mice. The complement protein C3 was inhibited via the antagonist neutrophil inhibitor factor (NIF). Cognitive performance of mice was assessed via a spatial discrimination (SD) task with two thymidine analogue (IdU, CldU) injections administered to track different ages of new cells. Extracted brains were sectioned and processed for immunohistochemistry to examine neurogenesis, functional connectivity and neuronal activation corresponding to spatial pattern separation. Preliminary results indicate that female APOEε4 mice took more time to reach the criterion of the SD task compared to male APOEε4 mice. NIF treatment shows potential of protecting against this cognitive impairment. Analyses are ongoing to examine activation of new neurons at different time points in response to the SD task and functional connectivity across different brain regions. Our research findings will be important to reveal regulators of neurogenesis, and factors influencing cognition by sex and genotype. Identified mechanisms (complement system) may serve as potential therapeutic targets for sex- and genotype-dependent cognitive decline with aging.

Disclosures: X. Lin: None. **K. Go:** None. **J.E. Richard:** None. **P.A. Sheppard:** None. **N.W. Diekow:** None. **L.A. Galea:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer’s Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.18/C36

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

Support: ES100221
ES103359

Title: Synaptic Properties of Lag3 knockout in an adult 5XFAD model of Alzheimer's disease

Authors: T. T. VIERLING[1], *D. RADZICKI[2,3], D. R. HODOROVICH[1], E. R. GJONESKA[1], S. M. DUDEK[1];
[1]Neurobio. Lab., Natl. Inst. of Envrn. Hlth. Sci., Res. Triangle Park, Research Triangle Park, NC; [2]Neurobio. Lab., NIEHS/NIH, Durham, NC; [3]Neurobiology Lab, National Institute of Environmental Health Sciences, Research Triangle Park, Research Triangle Park, NC

Abstract: A commonly used mouse model of Alzheimer's disease (AD) is the 5XFAD mouse, which expresses human amyloid beta precursor protein and presenilin 1 transgenes with 5 AD-linked mutations (Oakley et al., 2006). These mice begin to develop evidence of neurodegenerative AD pathologies such as gliosis and β-amyloid (Aβ) plaque deposition as early as 2 months of age. Previous reports have described 5XFAD deficits in hippocampal-dependent memory tasks, reductions in synaptic transmission in hippocampal area CA1, and impaired long-term potentiation (LTP) at Schaffer collateral synapses (Kimura & Ohno, 2009) by 6 months of age. Lymphocyte-activation gene 3 (Lag3) is expressed by immune cells, microglia, and neurons and may play a role in limiting neurodegenerative disease progression. For example, a widespread Lag3 knockout rescues Parkinson's disease (PD) pathology by decreasing spread of misfolded α-synuclein between neurons (Mao et al., 2016). Recent work has implicated immune processes in AD-like neurodegeneration, so we asked if genetic deletion of the Lag3 gene impacts LTP and other synaptic properties in the 5XFAD mouse model. Four groups of mice were tested: wild type (WT), 5XFAD, Lag3 knockout (Lag3KO), and a Lag3KO/5XFAD cross. At 6 months of age, we recorded extracellular field responses from the stratum radiatum of hippocampal area CA1 following electrical stimulation of CA3 axons, a synapse which typically shows robust LTP. Similar to previous work, we found that 5XFAD mutants show trends towards a reduction in evoked synaptic responses when compared to WT animals. We observed no differences in paired-pulse ratio, post-tetanic potentiation (PTP), or LTP when comparing 5XFAD mice to WT. Furthermore, the deletion of Lag3 in 5XFAD mice did not appear to rescue any of the observed deficits. Lag3KO/5XFAD mice showed a significantly higher paired pulse ratio than WT mice, indicating that presynaptic function may be altered in Lag3KO/5XFAD mice. Synaptic deficits may also be more pronounced in older mice, which are more affected by the progression of AD-typical pathology, so further experiments in 10-month-old mice will be informative. In summary, our results thus far suggest that loss of the Lag3 gene is likely to be insufficient to ameliorate synaptic deficits in 6-month-old 5XFAD mice.

Disclosures: T.T. Vierling: None. **D. Radzicki:** None. **D.R. Hodorovich:** None. **E.R. Gjoneska:** None. **S.M. Dudek:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.19/C37

Topic: F.04. Neuroimmunology and Neurovirology

Support: RO1GM128008.

Title: The dorsal motor nucleus of the vagus has impaired functional integrity in the 5xFAD Alzheimer's disease mice in an age and sex-dependent manner

Authors: *A. FALVEY[1], S. PALANDIRA[2], S. S. CHAVAN[3], M. BRINES[4], K. J. TRACEY[5], V. A. PAVLOV[4];

[1]The Feinstein Inst. for Med. Res., New York, NY; [2]Biomed. Sci., The Feinstein Inst. for Med. Res., Manhasset, NY; [3]Inst. for Bioelectronic Med., Feinstein Inst. For Med. Res., Manhasset, NY; [4]The Feinstein Inst. for Med. Res., Manhasset, NY; [5]Res. Admin., Feinstein Inst. For Med. Res., Manhasset, NY

Abstract: The inflammatory reflex is an endogenous vagus-nerve mediated pathway that regulates inflammation. The efferent motor-arm of this reflex arises from the cholinergic brainstem nucleus - the dorsal motor nucleus of the vagus (DMN). The vagus nerve can be targeted with electrical stimulation at various 'interfaces', including the DMN, to attenuate multiple inflammatory disorders in preclinical settings. These insights culminated in successful and ongoing clinical trials in patients with rheumatoid arthritis and Crohn's disease. Recently, it has been considered that targeting the inflammatory reflex can be considered as a therapeutic approach in Alzheimer's disease (AD). AD is a progressive age-related neurodegenerative disorder with an estimated 55 million affected individuals worldwide. While the exact disease pathogenesis remains enigmatic, there is abundant evidence for early and deleterious forebrain cholinergic neurodegeneration which plays a major role. Yet, it remains unknown if cholinergic deterioration extends to the brainstem and the cholinergic neuron rich DMN.

To assess the functional integrity of the DMN, we studied the anti-inflammatory efficacy of electrical DMN stimulation (eDMNS) in male and female 5xFAD mice (a widely used model of AD) and age-matched wild type (WT) littermates at ages 2, 6, or 10 months during endotoxemia. Mice were anesthetized and positioned in a stereotaxic frame. A concentric bipolar electrode was precisely guided to the coordinates of the left DMN, where eDMNS (50 μA, 30 Hz, for 5 mins) or sham stimulation was administered. Following this procedure, all mice were intraperitoneally injected with lipopolysaccharide (LPS: 0.5 mg/kg). After 90-minutes mice were euthanized, and blood samples were collected for serum cytokine analysis.

In 2-month-old male mice, eDMNS significantly reduced LPS-induced serum TNF levels compared to sham stimulation in both WT and AD mice. Similarly, at 6 months of age, eDMNS attenuated serum TNF levels in male WT and AD mice. However, by 10 months, eDMNS did not lower serum TNF levels in male AD mice but remained effective in WT mice. In females aged 2 months, eDMNS significantly suppressed serum TNF levels in both WT and AD mice during endotoxemia. At 6 months, however eDMNS reduced serum TNF levels in endotoxemic female WT mice, but not in AD mice. We observed similar effects in female 10 months-old mice.

These results demonstrate that the anti-inflammatory efficacy of eDMNS is impaired in AD suggesting functional impairment of these cholinergic neurons, which demonstrates that some brainstem cholinergic circuits are affected during AD in an age and sex-dependent manner.

Disclosures: A. Falvey: None. **S. Palandira:** None. **S.S. Chavan:** None. **M. Brines:** None. **K.J. Tracey:** None. **V.A. Pavlov:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.20/C38

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

Support: NIA RF1AG064859
NIA F32AG058456

Title: The trouble with Tribbles: Trib3 at the nexus of metabolism, neuroinflammation, and neurodegeneration

Authors: *D. J. BRAUN[1], E. GHONEIM[1], C. S. BAILEY[1], H. N. FRAZIER[2], L. J. VAN ELDIK[1];
[1]Univ. of Kentucky, Lexington, KY; [2]Sanders-Brown Ctr. on Aging, Univ. of Kentucky, Lexington, KY

Abstract: Tribbles homolog 3 (Trib3) is a sensor of metabolic stress that integrates fundamental metabolic and inflammatory pathways. Its expression is elevated in association with diabetic hyperglycemia both peripherally and centrally, and it is upregulated in the dopaminergic neurons most vulnerable to Parkinson's disease in humans and animal models. Further, Trib3 downregulation protects against amyloid beta induced cell death both *in vitro* and *in vivo*, and a recent imaging-genetics study suggests Trib3 may act as a mediator of characteristic gray matter loss in Alzheimer's disease (AD) patients. We have found elevated levels of Trib3 protein in the brain of a variety of mouse AD models, particularly in regions sensitive to AD-type change, such as the hippocampus. Interestingly, Trib3 levels may be modulated by some of our experimental anti-inflammatory compounds, which also serve to reduce neural dysfunction in these same preclinical models of AD. Some of the compounds are additionally able to normalize metabolism of microglial-type cells following pro-inflammatory insult *in vitro.* The convergent roles of Trib3 on metabolic and neuroinflammatory activation in AD-related neurodegenerative change is currently being defined in the context of anti-inflammatory treatment. Results from these studies will help to define the therapeutic potential of Trib3 as a target for AD-associated neurodegenerative changes and potentially other neurodegenerative processes more broadly.

Disclosures: D.J. Braun: None. **E. Ghoneim:** None. **C.S. Bailey:** None. **H.N. Frazier:** None. **L.J. Van Eldik:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.21/C39

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

Support: JSPS KAKENHI JP22K20692
JSPS KAKENHI JP23K06310
JSPS KAKENHI JP20K07743

JSPS KAKENHI JP21H02592
JSPS KAKENHI JP23K20044
AMED JP15dm0207001
AMED JP21dm0207112
JST JPMJMS2024
JST JPMJFR204D

Title: Plaque-associated endogenous IgG affects immunohistochemical detection of mouse monoclonal IgG antibodies in Alzheimer's disease mouse models

Authors: *S. ITO[1,2], K. YAMAUCHI[1,2], H. HAMA[5], M. KOIKE[2,3], A. MIYAWAKI[5,6], H. HIOKI[1,2,4];
[1]Dept. of Neuroanatomy, Grad. Sch. of Med., [2]Dept. of Cell Biol. and Neuroscience, Grad. Sch. of Med., [3]Advanced Res. Inst. for Hlth. Sci., [4]Dept. of Multi-Scale Brain Structure Imaging, Grad. Sch. of Med., Juntendo Univ., Tokyo, Japan; [5]Lab. for Cell Function Dynamics, RIKEN Ctr. for Brain Sci., Wako, Saitama, Japan; [6]Biotechnological Optics Res. Team, RIKEN Ctr. for Advanced Photonics, Wako, Saitama, Japan

Abstract: Experimental studies for Alzheimer's disease (AD), the most prevalent cause of dementia, have largely depended on transgenic mice that cause β-amyloidosis in their brains. Immunohistochemistry (IHC) is an indispensable technique for experimental and clinical research of AD. Here, we report plaque associated endogenous immunoglobulin G (IgG) (PA-IgG) and its impact on indirect immunohistochemical detection of mouse monoclonal IgG antibodies (Ms monoclonal IgG Abs) in the brain of AD mouse models. Immunostaining for Ms IgG in the brain of AD mouse models demonstrated endogenous IgG in the brain parenchyma accumulated on microglial cells associated with amyloid β (Aβ) plaques and/or Aβ plaques themselves. This PA-IgG caused robust off-target binding of secondary Abs against Ms IgG (H+L) in indirect IHC using Ms monoclonal IgG Abs. Blocking with Fab fragments of anti-Ms IgG (H+L) Ab was not effective for the off-target binding. Unexpectedly, we found that secondary Abs that specifically recognize Ms IgG1, 2a, 2b and 3 did not cause off-target binding on frozen brain sections of *App*$^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice, and allowed for specific labeling of Ms monoclonal IgG Abs in the AD mouse model brains. Finally, we demonstrated that indirect detection with a conventional secondary Ab against Ms IgG (H+L) Ab could lead to erroneous conclusions regarding Aβ plaque burden and phosphorylated tau accumulation in $^{AppNL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice, and the use of Ms IgG subclass specific secondary Abs allowed to avoid the erroneous conclusion caused by the endogenous IgG accumulation. Specific indirect detection of Ms monoclonal IgG Abs in AD mouse models by the use of secondary Abs against Ms IgG subclass would accelerate AD research by expanding the choice of Abs available for histochemical analysis in AD studies.

Disclosures: S. Ito: None. **K. Yamauchi:** None. **H. Hama:** None. **M. Koike:** None. **A. Miyawaki:** None. **H. Hioki:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.22/C40

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

Support: Weston Family Foundation

Title: Srsf3 acts as a regulator of innate immune response in a model of alzheimer's disease

Authors: *V. COELHO[1], H. BOUTEJ[2], S. DJEBBAR[3], J. KRIZ[4];
[1]CERVO Brain Res. Ctr., Universtité Laval, Québec, QC, Canada; [2]CRIUSMQ, Le Ctr. De Recherche De L'Institut Univ., Quebec, QC, Canada; [3]Univ. Laval, Québec, QC, Canada; [4]Psychiatry and Neurosci., Univ. Laval, Quebec, QC, Canada

Abstract: Chronic deregulation of innate immunity likely plays a key element in Alzheimer's Disease (AD) pathobiology. However, the precise mechanisms underlying the transition of microglia from beneficial to harmful phenotype in AD remains unclear. Accumulating evidence has emphasized that rebalancing and/or strengthening the innate immune response may be therapeutically relevant. We recently described a novel ribosome-based regulatory mechanism that controls innate immune gene translation in activated microglia orchestrated by the RNA binding protein SRSF3. Here, we aim to investigate SRSF3's role as a regulator of microglial innate immune response in AD. The experiments were performed using the APPswe/PS1 mouse model. The expression levels of SRSF3, its active form pSRSF3 and disease-associated microglial markers were analysed at different time point of disease. The levels of pSRSF3/SRSF3, Abeta, phagocytic, pro-inflammatory and neuronal markers were evaluated by western blot and ELISA while mice cognition was assessed by behavioural tests. Our results revealed that the observed increase in pSRSF3/SRSF3 levels correlated with disease progression and was restricted to IBA1 positive cells in the brain. Targeting SRSF3 by antisense morpholinos delivered intranasally induced a marked knockdown of endogenous protein (50-60%). Treatment with anti-SRSF3-Morpho initiated at 12 months of age decreased the levels of Abeta peptides and increased the expression of microglial markers including LILRB4, TREM2, increased expression of TLR2 and restored the recognition memory. Together, our findings suggest that targeting SRSF3 may open new avenues for therapeutic modulation of microglial response in AD.

Disclosures: V. Coelho: None. **H. Boutej:** None. **S. Djebbar:** None. **J. Kriz:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.23/C41

Topic: B.09. Glial Mechanisms

Support: Brain Disease Foundation

Title: The role of inflammasome priming in a CLN2 mouse model of inflammation

Authors: *K. SANCHEZ, M. S. DOMOWICZ, N. B. SCHWARTZ;
Pediatrics, Univ. of Chicago, Chicago, IL

Abstract: Neuronal Ceroid Lipofuscinoses, (NCLs or Batten disease) are a group of pediatric, early onset, fatal neurodegenerative diseases associated with mutations in 13 genes. All forms of the disease are characterized by lysosomal accumulation of fluorescent storage material called lipofuscin and profound neurodegeneration. The classical late-infantile NCL (cLINCL) in humans, caused by mutations in the CLN2/TPP1 gene, is usually diagnosed between 2-4 years of age with onset of seizures. Due to severe neurological deterioration typical of NCLs, most patients die between 7 and 15 years old. An underappreciated component of pathology includes central nervous system inflammation. Using the tripeptidyl peptidase 1 (Tpp1) deficient murine model (*Tpp1−/−*) to replicate the human disorder, inflammatory genes associated with microglia were found to be upregulated between 3 and 4 months of age. It is unknown how genes associated with the inflammasome are impacted in the context of priming and activation in the *Tpp1 -/-* mouse since lipofuscin is a danger-associated molecular pattern that accumulates in microglia. In naïve microglia, priming occurs when a pattern recognition receptor senses misfolded protein aggregates that initiate a MYD88-dependent signal transduction cascade that leads to the nuclear translocation of NFκB where it upregulates proinflammatory genes including *IL1β*. Aggregated proteins are then phagocytosed and activate the inflammasome multiprotein complex; NLRP3, ASC, and caspase-1. After the inflammasome is formed, caspase-1 cleaves the inflammatory cytokine IL1β to promote its maturation. Here we report for the first time that genes such as *NLRP3*, *ASC*, *Caspase-1*, and *IL1β* are upregulated in 4-month-old *Tpp1−/−* cerebellum compared to controls (*Tpp1+/-*; n=3 per group; 3 independent experiments). We then corroborated the upregulation of *NLRP3*, *ASC*, and *IL1β* in an acute slice culture model. In the presence of lipopolysaccharide (LPS), *NLRP3*, *ASC*, and *IL1β* were elevated in the *Tpp1−/−* slices compared to controls in a dose-responsive manner (n=3 per group; 3 independent experiments), suggesting that the *Tpp1 -/-* tissue is primed. Additional data indicate that the NLRP3 specific inhibitor MCC950 may reverse the upregulation of genes such as *NLRP3* and *Caspase-1* in the *Tpp1 -/-* tissue (n=1 per group; 1 independent experiments), providing the basis for future investigations that will therapeutically target the inflammasome in NCLs.

Disclosures: K. Sanchez: None. **M.S. Domowicz:** None. **N.B. Schwartz:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.24/C42

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

Support: NIH grant R21 ES026515
NIH grant P30 AG010129
NIH grant P30 ES023513

Title: Mutations in amyloid precursor or presenilin proteins cause dysregulation in calcium signaling in T cells from TgF344-AD rats, a model of Alzheimer's disease.

Authors: N. UPPAL[1], A. E. VALENZUELA[2], P. J. LEIN[2], ***A. F. FOMINA**[1];
[1]Physiol. and Membrane Biol., [2]Mol. Biosci., Univ. of California, Davis, Davis, CA

Abstract: Alzheimer's disease (AD) is a neurodegenerative disease for which there is no effective treatment. Immune system dysfunction in the CNS and periphery is believed to be causative to the pathogenesis and progression of AD. Mutations in amyloid precursor or presenilin proteins, which cause familial AD (FAD), interfere with intracellular Ca^{2+} ($[Ca^{2+}]_i$) signaling in neurons, leading to synaptic impairment and neurodegeneration. We hypothesized that FAD causative mutations may affect peripheral immune responses via dysregulation of Ca^{2+} signaling in immune cells. Using the Ca^{2+} indicator dye Fura-2, we explored $[Ca^{2+}]_i$ dynamics in splenic T lymphocytes from fourteen-month-old transgenic TgF344-AD rats expressing mutant human amyloid precursor protein (APPsw) and presenilin 1 (PS1DE9). We found no differences in the resting Ca^{2+} levels or the releasable Ca^{2+} store content (measured as Ca^{2+} transients triggered by the SERCA blocker thapsigargin) between T cells from TgF344-AD rat (TG cells) and WT controls (WT cells). However, on average, the amplitude of Ca^{2+} transients elicited by the store-operated calcium entry (SOCE) was significantly larger in TG cells than in WT cells. The Mn^{2+} quench of Fura-2 fluorescence, which is proportional to the rate of SOCE, was significantly faster in TG cells than in WT cells. Preincubation of cells with 30 μM dantrolene, a ryanodine receptor blocker, reduced the amplitude of the SOCE-triggered Ca^{2+} transients and the rate of the Mn^{2+} quench in TG T cells. Given that $[Ca^{2+}]_i$ signaling drives T cell effector functions, upregulation of SOCE by mutations in amyloid precursor and presenilin proteins in T cells may affect peripheral immune responses and enhance systemic inflammation, thereby contributing to AD pathogenesis. We speculate that the previously described neuroprotective effect of dantrolene in AD animal models may be at least partially due to the normalization of the Ca^{2+} signaling and effector functions of peripheral immune cells.

Disclosures: **N. Uppal:** None. **A.E. Valenzuela:** None. **P.J. Lein:** None. **A.F. Fomina:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer’s Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.25/C43

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

Title: Cd36 scavenger receptor promotes adaptive T-cell CNS infiltration and neuroinflammation in AppSAA knock-in mouse model of Alzheimer's disease

Authors: *C. JASPER-DURUZOR[1], S. CISZ[1], B. SCOFIELD[2], P.-C. KUO[2], J. YEN[2]; [1]Biol. Sci., Purdue Univ. Fort Wayne, Fort Wayne, IN; [2]Dept. of Microbiology and Immunol., Indiana Univ. Sch. of Med., Fort Wayne, IN

Abstract: CD36 is a type B scavenger membrane protein with wide distribution in the body system. These receptors are commonly expressed by myeloid cells, such as macrophages and microglia, and endothelial cells, and they function in the cellular uptake of long-chain fatty acids and oxidized low-density lipoproteins. In Alzheimer's Disease (AD), hydrophobic amyloid beta fibrils bind to the CD36 scavenger receptor that induces microglial activation leading to the CNS proinflammatory responses. Microglial activation has been shown to promote the CNS infiltration of immune cells, including CD4+ and CD8+ T cells. This infiltration is detrimental to the brain because it exacerbates neuroinflammation and leads to the loss of synaptic-associated proteins and, ultimately, neuronal damage. Studies have also shown that neuroinflammation correlates to AD pathology, which comprises Aβ accumulation, tau phosphorylation, and cognitive decline associated with synaptic and neuronal loss. With this knowledge, we aim to elucidate the role of CD36 receptor in neuroinflammation using a novel AppSAA Knock-in AD model. To achieve that, AppSAA Knock-in mice were crossed with CD36KO mice to generate CD36KOAppSAA mice, while AppSAA mice served as control animals. At 7-8 months old, brain tissues were harvested from AppSAA and CD36KOAppSAA mice and subjected to 6E10-DAB staining to determine the Aβ area. In addition, mononuclear cells were isolated from the brains to assess CD4+ and CD8+ T cell infiltration and microglial activation. We observed a comparable level of Aβ accumulation in AppSAA and CD36KOAppSAA mice. In addition, we found microglial activation based on Celec7a expression was comparable between AppSAA and CD36KOAppSAA mice. However, our results showed a significant reduction of CD4+ and CD8+ T cells infiltrating into the brains of CD36KOAppSAA mice compared to those of AppSAA mice. Since CD36 receptors are highly expressed by microglia and brain endothelial cells, our results suggest that attenuated CNS CD4+ and CD8+ T cell infiltration in CD36KOAppSAA mice might be regulated by microglia and brain endothelial cells at the level of chemokine production and adhesion molecule expression, respectively. In summary, our findings suggest that the CD36 receptor may play a role in promoting neuroinflammation in AD through recruiting CNS infiltrating CD4+ and CD8+ T cells. Hence, targeting the CD36 receptor may represent a novel strategy in modulating T cell-mediated neuroinflammation in AD.

Disclosures: C. Jasper-Duruzor: None. **S. Cisz:** None. **B. Scofield:** None. **P. Kuo:** None. **J. Yen:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

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Program #/Poster #: PSTR013.26/C44

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

Support: PICT 2018-00648
Secyt 2018-33620180100579CB
PIP 2021 11220200102463CO

Title: Cyp46 in brain inflammation: a path to alzheimer's risk

Authors: *G. CATALDI;
Cell. and Mol. Neurobio., Inst. Ferreyra, INIMEC, Cordoba, Argentina

Abstract: Cholesterol 24-hydroxylase (or CYP46) carries out the hydroxylation of cholesterol to 24(S)HOC, which is the main mechanism of cholesterol elimination from the brain. CYP46 has been mainly reported in neuronal populations, however, in cases of brain damage such as traumatic brain injury or Alzheimer's disease CYP46 increases its expression in astrocytes. At the moment, the role that CYP46 would play in astrocytes in pathological conditions is unknown. We found that CYP46 levels are greatly increased in reactive astrocytes challenged with lipopolysaccharide (LPS) or the proinflammatory cytokine IL-6 which is released by astrocytes and microglia, when they are treated with LPS. In addition, our data show that IL-6 is able to increase APP synthesis in rat primary astrocytes by a mechanism mediated by CYP46. Indeed, the IL-6 ability to trigger APP synthesis in astrocytes is impaired by CYP46 inhibition. Further providing a link between CYP46 and APP, our results show a marked increase in APP levels in 24(S)HOC-treated primary cortical astrocytes compared to control cells. Our data indicate that the increase in APP mediated by 24 (S)HOC is of transcriptional origin. We demonstrate that in cortical astrocytes, 24(S)HOC does not affect the non-amyloidogenic pathway of APP, as it does not increase alpha-CTF fragments, while it does enhance the amyloidogenic processing of APP, generating beta-CTF fragments. Preliminary data show that treatment with 24(S)HOC also increases beta-amyloid production in vitro.We propose that under a proinflammatrory context, as for example a microbial infection in the brain, 24(S)HOC would mediate the production and processing of APP in astrocytes to face the aggression but on the other side it would predispose to Alzheimer's disease.

Disclosures: G. cataldi: None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.27/C45

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

Support: NIH Grant RF1NS122174-01

Title: Heightened infiltration of immune effector cell types in the hippocampal regions in the APP/PS1 mouse model of Alzheimer's disease

Authors: *M. MAYNES[1], K. AYASOUFI[3], C. A. OWENS[2], D. M. ANANI-WOLF[4], Z. P. TRITZ[5], F. JIN[2], M. J. HANSEN[2], A. J. JOHNSON[2];
[2]Immunol., [1]Mayo Clin., Rochester, MN; [3]Neurosurg., Duke Univ., Durham, NC; [4]Duke Univ. Sch. of Med., Durham, NC; [5]Microbiology, Univ. of Wisconsin - La Crosse, La Crosse, WI

Abstract: Alzheimer's disease (AD) is among the most common neurodegenerative diseases which a role for immune cells in its etiology is only beginning to be realized. AD has two molecular pathological hallmarks that are believed to drive the disease which is the presence of amyloid beta (Aβ) plaques and phosphorylated tau tangles within neuronal cells. The amyloid plaques can be modeled in mice by inserting transgenes to create human Aβ plaques inside the mouse brain to model the disease. Amyloid precursor protein (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-dE9) are two transgenes inserted into C57BL/6 mice that results in Aβ plaques in the hippocampus and cortex. This mouse is known as the APP/PS1 mouse. Immune cell infiltration into the brain is associated with aged APP/PS1 mice as well as in humans with AD. However, comprehensive immune profiling has not been performed in this model to outline immune cell effectors potentially involved in neuropathology. Therefore, we employed spectral flow cytometry to investigate the immune cell profile in 24-month-old APP/PS1 mice compared to an age matched control. We found that there are increased numbers of CD8 T, γδ T, and NK cells expressing perforin and other activation related surface markers. Using small animal MRI imaging, we also observed enlarged lateral, dorsal, and ventral ventricles in the brains of these APP/PS1 mice when compared to wildtype age matched control. These results provide insight into the regional immune cell infiltration of the brain, setting the stage for further analysis of immune mechanisms of neuropathology in experimental AD.

Disclosures: M. Maynes: None. **K. Ayasoufi:** None. **C.A. Owens:** None. **D.M. Anani-Wolf:** None. **Z.P. Tritz:** None. **F. Jin:** None. **M.J. Hansen:** None. **A.J. Johnson:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer’s Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.28/C46

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

Support: SBIR Grant R43MH122070

Title: Brain-wide quantification of amyloid plaques and neuroinflammation in AD model mice

Authors: N. GUANZON[1], Y. GALLEGOS[1], ***C. REDD**[1], E. CASTILLO[1], E. BLAES[1], R. AZEVEDO[2], S. P. GANDHI[3], D. G. WHEELER[4];
[1]Translucence Biosystems, Irvine, CA; [2]UC Irvine, Irvine, CA; [3]Neurobio. and Behavior, Univ. of California, Irvine, CA; [4]Translucence Biosystems Inc, Irvine, CA

Abstract: Traditional histological methods have long been fundamental to neuroscience research. However, imaging deep into tissues has historically required slicing and mounting on

slides, limiting observations to predefined regions of interest. Recent advances in optical clearing and light sheet imaging have opened an exciting new avenue for brain-wide, cellular resolution immunostaining at the forefront of a dimensional shift from 2D to 3D histology. One area where these methods have particular utility is in the development of CNS therapeutics where they can be used to examine brain-wide target engagement and phenotypic efficacy. Toward this end, we have focused on Alzheimer's Disease models, developing clearing, imaging, and quantification methods for brain-wide regional quantification of amyloid plaques and microglia. Using our optimized iDISCO-based tissue clearing method and our Mesoscale Imaging System for ZEISS Lightsheet microscopes, we can image micron-scale resolution immunoreactivity across entire intact mouse brains in <20 min. Further, our AI-powered software, the Translucence Teravoxel Toolkit (3TK), identifies individual immunostained cells throughout the brain and aligns them to the Allen Reference Atlas to produce an unbiased, regionalized read-out of cellular patterns across 100's brain areas. Using antibodies targeting the microglial protein Iba1, we can label microglia across the entire brain. We have developed multiple workflows to segment microglia, providing metrics of shape and microglial activation. In LPS-treated mice we have quantified the activation of microglia with traditional 2D immunohistochemistry and with 3D tissue clearing, demonstrating that our AI powered quantification provides brain-wide measurements that are typically made in brain regions of interest. We have also trained machine learning algorithms to identify 6E10 antibody-labeled β-Amyloid throughout the brain and differentially quantify amyloid immunoreactivity in plaques and neuronal cell bodies. In 5xFAD Tg model mice, rather than displaying the ramified morphology seen in WT mice, microglia become condensed and colocalize with β-Amyloid plaques. Our automated methods segment and quantify these plaque-associated microglia (PAMs) throughout the brain. This technology is now being disseminated with our BRAIN Initiative-funded iDISCO-based tissue clearing kits and cloud-based quantification pipeline, enabling neuroscientists to easily employ next generation 3D immunohistochemistry for unbiased, complete, and anatomically precise mapping of the efficacy of CNS therapeutics affecting amyloid deposition and neuroinflammation.

Disclosures: N. Guanzon: A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **Y. Gallegos:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **C. Redd:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **E. Castillo:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **E. Blaes:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **R. Azevedo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **S.P. Gandhi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **D.G. Wheeler:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of

intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.29/C47

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

Support: NIA Grant AG064244
NIA Grant AG070075

Title: Immunoproteasome Impairment Exacerbates Alzheimer's Disease Pathology and Modulates Neuroinflammatory Responses

Authors: *D. E. LORMAN[1], M. KUMAR[1], S. JIANG[2], M. SRIKANTH[2], N. MYEKU[3]; [1]The Taub Inst. for Res. on Alzheimer's Dis. and the Aging Brain, [2]Taub Inst. for Res. on Alzheimer's Dis. and the Aging Brain, Columbia Univ. Irving Med. Ctr., New York, NY; [3]Pathology and Cell Biol., Taub Inst. for Res. on Alzheimer's Dis. and the Aging Brain, Columbia Univ. Med. Ctr., New York, NY

Abstract: Alzheimer's disease (AD) is a debilitating neurodegenerative disease that is pathologically characterized by impairment of the ubiquitin-proteasome system. Induction and assembly of the immunoproteasome (IP), the inducible form of proteasomes present in immune cells, have been observed in AD. However, the role of the IP in AD etiology is unclear. We conducted immunostaining of PS19 and AD knock-in (KI) mice crossed to immunoproteasome deficient mice (L7M1) to evaluate whether deficient IP exacerbates AD pathology. A combination of immunohistochemical markers were used to stain tissue for tau and amyloid (n=6, three slices each). Additionally, the IP has been implicated in modulating neuroinflammatory responses observed in AD. We used microglial markers Iba1 and CD11 to measure microglial morphology and activation, respectively, in the presence and absence of the IP. Immunofluorescence signal was quantified by Fiji-2/ImageJ. IMARIS software was utilized to visualize 3D renderings of interactions between representative microglia, tau, and amyloid in APP/hTau and L7M1/APP/hTau genotypes. We observed exacerbated tauopathy (ps202/pT205) in the CA1 region of the hippocampus of PS19/L7M1 mice compared to PS19 mice with functional IP. L7M1/APP/hTau mice demonstrated increased accumulation of PHF tau (ps396/ps404) and β-amyloid in the cortex, as well as hippocampal regions CA1 and dentate gyrus (DG) compared to APP/hTau mice. An increase in CD11 infiltration in the CA1 hippocampal region of PS19/L7M1 mice was observed relative to PS19 mice with IP. L7M1/APP/hTau tissue demonstrated increased activation and ramification of Iba1 stained microglia compared to APP/hTau tissue in the CA1, DG, and cortical regions. Representative 3D renderings by IMARIS show morphological differences in microglia between L7M1/APP/hTau and and APP/hTau genotypes, as well as internalized p-tau within the soma of microglia in IP

deficient tissue. Increases in tau and amyloid observed in IP deficient genotypes suggest that impaired protein clearance by the IP exacerbates amyloid and tau pathology in AD. Activated microglia observed in IP deficient genotypes point to a link between impaired IP and innate immunity.Overall, these results suggest that the IP has a significant protective role in limiting amyloid and tau pathology. Associations between microglial activation and impaired IP function can help decipher the dynamic interplay between neuroinflammation and the IP. The results from this study aid in elucidating the functional role of the IP in AD and can be used to identify the IP as a target for therapeutic intervention in aging and cognitive decline.

Disclosures: D.E. Lorman: None. **M. Kumar:** None. **M. Srikanth:** None. **N. Myeku:** None.

Poster

PSTR013: Neural-Immune Signaling in Alzheimer's Disease

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.30/C48

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

Support: AG065406
NS105984
p30AG066509
p50 AG005136

Title: Activation of proinflammatory and ferroptosis related pathways in a novel mouse model of Alzheimer's disease and vascular dementia

Authors: *P. A. ADENIYI[1], K. FOPIANO[2], V. BUNCHA[3], L. LANG[4], X. GONG[5], D. MIZAN[5], J. A. FILOSA[3], S. A. BACK[5,6], Z. BAGI[7];
[1]Departments of Pediatrics, Oregon Hlth. & Sci. Univ., Portland, OR; [2]Departments of Physiol., Med. Col. of Georgia at Augusta Univ., Augusta, GA; [3]Departments of Physiol., Augusta Univ., Augusta, GA; [4]Departments of Physiol., Augusta Univ., Augusta, OR; [5]Departments of Pediatrics, Oregon Hlth. and Sci. Univ., Portland, OR; [6]Neurol., Oregon Hlth. and Sci. Univ. (OHSU), Portland, OR; [7]Departments of Physiol., Med. Col. of Georgia Augusta Univ., Augusta, GA

Abstract: Hypertensive heart disease (HHD) is associated with an increased risk for vascular dementia (VCID) and Alzheimer's disease (AD). The mechanisms through which HHD, VCID, and AD interact to cause dementia to remain incompletely understood. We hypothesized that worsening cognitive decline in AD is related to progressive cerebrovascular dysfunction from HHD. To define interactions between HHD and AD, we developed a novel mouse model where the chimeric mouse/human APP with the Swedish mutation and human PSEN1 lacking exon 9 (APP/PS1) was combined with experimental HHD (uninephrectomy with 9-week aldosterone infusion). Consistent with worsening cognitive decline, 6-month-old APP/PS1 mice with HHD exhibited lower performance in the novel object recognition (NOR) test than aged-matched

APP/PS1 mice. Using 2-photon imaging of penetrating cerebral arterioles, we observed impaired whisker stimulation-induced neurovascular coupling and diminished bradykinin-induced vasodilation in APP/PS1 mice with HHD compared to age-matched APP/PS1 mice. Accelerated cognitive dysfunction and cerebrovascular dysfunction in mixed HHD were associated with increased levels of pro-inflammatory mediators, including CXCL13/16 and LIX, CXCL, TNF, IL-1, and IL-6 compared to aged-matched APP/PS1 mice. Moreover, immunohistochemical analyses demonstrated an increase in reactive astrogliosis and microgliosis in APP/PS1 mice with HHD. Moreover, proteomic analyses demonstrated elevated levels of ferroptosis markers and activation of ferroptosis pathways in the brains of APP/PS1 mice with experimental HHD. Overall, our findings suggest a role for activation of proinflammatory and ferroptosis-related pathways in AD and HHD. This novel animal model provides unique access to define interactions between AD and cerebrovascular disease that contribute to progressive cognitive decline.

Disclosures: P.A. Adeniyi: None. **K. Fopiano:** None. **V. Buncha:** None. **L. Lang:** None. **X. Gong:** None. **D. Mizan:** None. **J.A. Filosa:** None. **S.A. Back:** None. **Z. Bagi:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.01/C49

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

Title: Temporal progression of Ferritin in the cortex and hippocampus of Alzheimer’s disease rat

Authors: *S. SARKAR[1], K. ROOKS[2], J. B. RAYMICK[3];
[1]Neurotoxicology, Natl. Ctr. for Toxicological Research/ US FDA, Jefferson, AR; [2]DNT, NCTR, Little Rock, AR; [3]Neurotoxicology, Natl. Ctr. For Toxicology/ US FDA, Jefferson, AR

Abstract: Excessive deposition of amyloid-beta (Aβ) plaques and neurofibrillary tangles are two salient features of Alzheimer disease (AD). The accumulation of metals in amyloid plaques has been suggested to play an important role in the development of Alzheimer’s pathology. To establish a causative relationship, this study examines the buildup of the protein Ferritin within the microglia of the brain. Ferritin is an important protein that maintains iron homeostasis by oxidizing the metal into less reactive species. Ferritin has two isoforms, one that is H-rich, and one that is L-rich. Central Nervous system microglia contain L-rich ferritin. To determine a correlation between buildup of iron within amyloid plaques, and the progression of AD Pathology across different age groups of animals of both sexes (6, 16 and 20 months) was studied. Ferritin was visualized by using light-microscopic immunohistochemistry, and Congo red was used to determine whether deposition of ferritin was related to the deposition of amyloid plaques. In AD transgenic rats, area occupied by ferritin increased with time in both the cortex and hippocampus. In non-transgenic rats, there was no discernable trend in the variation of ferritin across different age groups. In both male and female rats at 6 months of age, ferritin was

ubiquitously present in the brain. Most of the cortical and hippocampal ferritin were of microglial type with cell bodies exhibiting intense processes. On the other hand, the thalamus, striatum, and amygdala show circular ferritin positive glial cells with no apparent processes. In the transgenic AD rat, ferritin in the cortex was seen proliferated around the plaques and hippocampus in both sexes compared to their non-TG counterparts. Two-way ANOVA using sex, genotype, and age as factors indicates a statistically significant increase in ferritin in both the hippocampus and cortical regions of transgenic rats with increasing age. Given that ferritin was higher around amyloid plaques, suggests that this increase in ferritin does contribute to Alzheimer's pathology and that manifestation of AD could be due to causative metal deposition throughout the plaques.

Disclosures: S. Sarkar: None. **K. Rooks:** None. **J.B. Raymick:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.02/C50

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

Support: 1R21AG075393

Title: Targeting AD-pathology by increasing Angiotensin (1-7) via genetically modified probiotic in TgF344-AD rats

Authors: *A. BANERJEE[1], B. FORD[1], M. BAGLEY[4], T. W. BUFORD[2], L. L. MCMAHON[5], A. HERNANDEZ[1,3];
[1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]Univ. of Alabama at Birmingham, Birmingham, AL, ; [3]Med-GGPC, Univ. of Alabama at Birmingham, Birmingham, AL; [4]Med. Univ. of South Carolina, Charleston, SC, ; [5]Univ. of Virginia, Charlottesville, VA.

Abstract: To date, proven treatments for preventing age- and AD mediated cognitive decline are lacking, thus research on potentially efficacious interventions is desperately needed. This work approaches the treatment of AD-related neuropathological, synaptic, and cognitive decline through increased angiotensin (Ang) 1-7. Ang (1,7) binds Mas receptors expressed in multiple cell types within the brain, which can decrease inflammation and AD pathology. While previous attempts at sustaining increased levels of Ang1,7 have proven difficult, as traditionally this requires repeated injections or continuous infusions, the work presented herein utilizes a genetically modified probiotic (Lactobacillus paracasei secreting Ang (1,7); LP-A) that can be delivered orally to chronically increase Ang (1,7). LP-A colonizes in the gut microbiome, increases circulating Ang (1,7) and decreases cytokines in the brain of rats. Moreover, it improves cognitive performance in a drosophila model of AD. Therefore, we utilized LP-A to assess the capability of a sustained increase in Ang1,7 to ameliorate cognitive and pathological deficits in a transgenic rat model of AD, the TgF344-AD rat. Behavioral performance was

assessed on a variety of behavioral tasks, including measures of associative learning, spatial navigation, object recognitive memory, fear conditioning and anxiety-like behavior in TgF344-AD rats given Lactobacillus paracasei or the genetically modified LP-A, relative to TgF344-AD and wildtype rats given saline. Brain slice electrophysiology in the dentate gyrus was used to assess strength of basal transmission and long-term plasticity. LP-A administration significantly altered gut microbiome composition and can modify behavioral performance. Thus, utilizing this approach may be an appropriate avenue for the treatment of AD-related symptomology in future clinical trials.

Disclosures: A. Banerjee: None. **M. Bagley:** None. **T.W. Buford:** None. **L.L. McMahon:** None. **A. Hernandez:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.03/C51

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

Support: R01AG066489
1F99NS139543

Title: Investigating the effects of increased O-GlcNAcylation on glial cell morphology and noradrenergic innervation in TgF344-AD rats

Authors: *M. GARCIA[1,2], L. L. MCMAHON[3];
[1]Univ. of Alabama, Birmingham, Birmingham, AL; [2]Dept. of Neuroscience, Medical University of South Carolina, Charleston, SC; [3]Dept. of Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Alzheimer’s disease (AD) pathology accumulates 20-30 years before cognitive symptoms appear. During this time, there are increases in inflammation, amyloid-β (Aβ), and hyperphosphorylated Tau. Previous preclinical studies have shown that the post-translational modification, O-GlcNAcylation, which involves the addition of a single N-acetylglucosamine moiety to serine or threonine residues, can decrease amyloidogenic processing of amyloid precursor protein (APP) and compete with phosphorylation of specific serines on Tau, thereby decreasing its accumulation. In addition, protein O-GlcNAcylation has anti-inflammatory effects. This study is designed to evaluate how pharmacologically increasing O-GlcNAcylation via inhibition of O-GlcNAcase (OGA), the enzyme that removes O-GlcNAc moieties, impacts the progression of AD pathology using the TgF344-AD rat model, the most comprehensive AD rat model to date. This work is significant since OGA inhibitors are currently in AD clinical trials. To increase O-GlcNAcylation we used the highly selective OGA inhibitor thiamet-G (TMG; 10mg/kg s.c) administered 3x/wk for 3 months (n=8-10/gp). We chose 6-month-old TgF344-AD (Tg) rats and non-transgenic (non-Tg) littermates since pathology is already significant at this

age. Preliminary results confirm significant increases in GFAP, Iba1, and amyloid-β in Tg+saline compared to non-Tg+saline rats. Importantly, GFAP and Iba1 protein levels in Tg+TMG are not significantly different from non-Tg+saline rats. Using tyrosine hydroxylase (TH) immunohistochemistry and confocal imaging we examined the density of noradrenergic innervation in the dentate gyrus and found a significant decrease in TH+ axons in Tg+saline rats compared to non-Tg+saline, confirming our previous findings. Unexpectedly, we found that increasing O-GlcNAcylation led to an increase in TH+ axon density in non-Tg+TMG compared to non-Tg+saline, with no significant differences observed in either Tg treatment groups. Tg animals did have an increase in abnormal TH innervation in the hilus of the dentate gyrus compared to non-Tg rats. These studies shed light on how increasing O-GlcNAc in non-Tg and Tg animals affects noradrenergic innervation and amyloid pathology, which could give further insights into the current clinical trials.

Disclosures: M. Garcia: None. **L.L. McMahon:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.04/C52

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

Support: R21-MH121723-S1

Title: Retinal regulation of Locus coeruleus: a chemogenetic approach to treat neurodegenerative disorders

Authors: *S. DELCOURTE[1,2], G. CROZIER[2], G. S. ASTON-JONES[2];
[1]Rutgers Univ. RBHS, Piscataway, NJ; [2]Brain Hlth. Inst., Brain Hlth. Inst. Rutgers Univ., Piscataway, NJ

Abstract: Alzheimer’s Disease (AD) is the most prevalent form of dementia. Clinical studies show that abnormal accumulation of tau protein in the brain nucleus locus coeruleus (LC) may play an early role in AD progression. Using an animal model of AD with this early LC tau pathology, the Tg-F344 AD rat, Rorabaugh et al. (2017) showed that specific chemogenetic activation of LC rescued impaired reversal learning. Given its deep location in the brainstem, LC is difficult to access in humans, limiting this approach for clinical application. Suprachiasmatic nucleus (SCN) provides an indirect input to LC via a relay in dorsomedial hypothalamus (DMH) (Aston-Jones et al., Nat. Neurosci. 2001). SCN is therefore in a key position to integrate light information with LC, via a circuit we denote as the Photic Regulation of Arousal and Mood (PRAM) pathway: retina ->SCN ->DMH ->LC (Bowrey & Aston-Jones, Anxiety Depress. 2017). Here, we tested whether PRAM activation would mitigate learning deficits in the Tg-F344 AD rat model. Methods: 6-month-old Tg-F344 or WT rats received intravitreal injections of an AAV encoding a Gq DREADD (AAV2-hSyn-hM3D(Gq)-mCherry) or control virus

(AAV2-hSyn-EGFP). 3 months later, we assessed the effects of retinal DREADD stimulation on learning and memory in Tg-F344 rats using the Morris Swim Maze (MWM). Rats learned the location of the platform over 4x1min sessions daily for 6 days and were then subjected to a referral (extinction) session and 4 reversal sessions (new platform location). Injections of the DREADD agonist clozapine-N-oxide (CNO; 2mg/kg, ip) were given 30min before acquisition, referral and reversal sessions. Results: Electrophysiological and Fos analyses showed that Gq DREADD retinal stimulation increased retinal ganglion cell, SCN, DMH and LC neural activities. Neither intravitreal injections nor retinal activation decreased visual acuity. Tg-F344-AD rats showed poor initial as well as reversal learning. Retinal DREADD stimulation reduced the learning deficit in the Tg-F344-AD rats during acquisition, improved recall during referral and decreased reversal deficits during reversal. Those effects were more pronounced in female TgF344-AD rats. Conclusions: Learning and memory deficits in Alzheimer disease, associated with dysregulation of the noradrenergic LC, can be attenuated by PRAM-induced activation of LC. The PRAM pathway is a novel and relatively non-invasive approach to treating AD and other neuropsychiatric disorders linked to LC function.

Disclosures: S. Delcourte: None. **G. Crozier:** None. **G.S. Aston-Jones:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.05/C53

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

Support: Jeanne Kempner Fellowship (C.N.)
AARG-17-533363, NIA R21 – AG059223
NIA R01 – AG063945

Title: Addressing whether PLD1 inhibition is more effective against astrocytic or neuronal pathology in Drosophila melanogaster 3xTg-AD flies

Authors: *K. H. GARZA[1], S. SREENIVASA MURTHY[2], B. KRISHNAN[3];
[2]Neurol., [3]Dept. of Neurol., [1]Univ. of Texas Med. Br., Galveston, TX

Abstract: Alzheimer’s Disease (AD) and related disorders (ADRD) are a prevalent source of concern in the quality of life among the aging population. It is the 6th leading cause of death and has no reliable cure. PLD1 (phospholipase D1) is a lipolytic enzyme that in recent studies has been observed to be aberrantly elevated in the hippocampus in AD patients. Previous research has found that PLD1 inhibitor (VU0155069) was effective in preventing memory deficits in 3xTg-AD mice. However, studies to discover the impact of astrocytic or neuronal overexpression of PLD1 remains to be explored. **The current study will use a unique pharmacological approach in *Drosophila melanogaster*** as a preamble to overexpressing human PLD1 gene in Alzheimer’s Disease background using different transgenic models to validate the therapeutic

potential. Fruit flies (*Drosophila melanogaster)* were used due to their short life span (6 to 12 weeks), diurnal sleep patterns and since they express 60% of human disease genes. The approach is poised **to address whether PLD1 inhibition is more effective against astrocytic or neuronal pathology. Methods:** Genetically modified flies UAS-3xTG (BDSC#33799) driven by either elav- GAL4 (BDSC#458) or repo-GAL4 (BDSC #7415), we provided them with saline (0.9% NaCl) or inhibitor (VU0155069 @ 1mg/kg). Multiple assays were used to determine the health of the flies. These experiments tested the analogous parts between humans and flies. Mass Spectrometry: Used to test how much of the drug was in the flies' system. 1.Electroretinogram (ERG): Measures the electrical response of the fly eye, which can gauge neuronal degradation. 2.Drosophila Sleep Monitor (DAM): Measures the amount of time the flies are resting. **Results:** Analyzing the data through statistical analyses (t-tests and 2-way ANOVA) the Mass Spectrometry data showed that when the flies were given the PLD1 inhibitor, the detected levels of the PLD1 inhibitor was significantly more than in saline treated. The ERG data represented a significant or close to significant difference in the response to light between inhibitor and saline in both glial and neuronal flies, with glial having more significant results overall. Finally, the DAM data represented the glial flies given inhibitor being the only flies to have a significant reduction in the amount of sleep during the day compared to saline treated. **Conclusion:** Overall inhibiting PLD1 was more effective in glial populations compared to neuronal pathological insults.

Disclosures: K.H. Garza: None. **S. Sreenivasa murthy:** None. **B. Krishnan:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.06/C54

Topic: C.01. Brain Wellness and Aging

Title: Kcc2 as a new potential pharmacological target to rescue cognitive decline of aging.

Authors: *A. CUCINELLI[1,4], I. COLOMBI[1], F. PICCARDI[2], M. BOLLA[1], M. BORGOGNO[3], M. DE VIVO[3], A. CONTESTABILE[1], A. SAVARDI[1], L. CANCEDDA[1];
[1]Brain Develop. and Dis., [2]Animal Facility, [3]Mol. Modeling and Drug Discovery, ISTITUTO ITALIANO DI TECNOLOGIA, Genova, Italy; [4]Univ. degli studi di Genova, Genova, Italy

Abstract: Aging is characterized by the susceptibility of individuals to a series of conditions that significantly affect their life quality as well as that of their families, and eventually lead to death. Frailty and decline of multiple vital systems are indeed typical of the aging process. Among the declining vital systems, also the central nervous system (CNS) can be affected, resulting in cognitive and memory deficits, dementia, sleep disturbances, and, in some cases, adverse reactions to benzodiazepines. To preserve intellectual performance in elderlies, a number of studies indicate that promoting neuronal synaptic plasticity may be fundamental. Certainly, the neurotransmitter GABA plays a crucial role in regulating brain plasticity through the modulation

of neuronal excitability, and alterations in GABAergic signaling have been already described during aging.The balance between excitation and inhibition in the CNS is fundamental for its development and optimal functioning, with defective and/or altered GABAergic signaling (through chloride (Cl^-)-permeable GABAA receptors) found implicated in diverse neurodevelopmental and psychiatric disorders. A pivotal role in maintaining the balance between neuronal excitation and inhibition through GABAA-receptor signaling is held by the Cl^- importer NKCC1 and exporter KCC2. Dysregulations or mutations of these two chloride transporters have been observed in a wide variety of brain conditions. In consideration of the relevant role played by NKCC1 and KCC2 in brain physiology and pathology, we investigated their expression in aging. We identified an altered expression of KCC2 in the hippocampus of aged mice (24 months old) and elderly people (>75 years old), when compared to control mice (2 months old) and young adult people (~ 25 years old). This led to an altered GABA signaling in vivo in mice. Pharmacological targeting of KCC2 by a commercial tool compound rescued the age-associated memory impairments in aged mice, which we observed in behavioral studies. Altogether, our studies indicate KCC2 as a possible target to rescue cognitive decline of aging.

Disclosures: **A. Cucinelli:** None. **I. Colombi:** None. **F. Piccardi:** None. **M. Bolla:** None. **M. Borgogno:** None. **M. De Vivo:** None. **A. Contestabile:** None. **A. Savardi:** None. **L. Cancedda:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.07/C55

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01AG059028

Title: Curcumin effects on ultrastructural changes in synapsis and mitochondria in middle-aged rhesus monkeys

Authors: *C. FREIRE-COBO[1], M. MEDALLA[2], M. VARGHESE[1], J. I. LUEBKE[2], P. R. HOF[1,3,4];
[1]Nash family Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Anat. & Neurobio., Boston Univ. Sch. of Med., Boston, MA; [3]Friedman Brain Institute, New York, NY; [4]Ronald M. Loeb Center for Alzheimer's Disease, New York, NY

Abstract: Elucidating the impact of aging on the structure and function of neurons is key to understand the mechanisms underlying synaptic dysfunction and ensuing susceptibility to age-related cognitive decline. The role of structural alterations in dorsolateral prefrontal cortex (DLPFC) pyramidal neurons affecting synaptic function has been extensively addressed in cognitive aging studies, although until recently, focusing mainly on aged individuals. New evidence shows that age-related changes in cognition can occur as early as the 4th and 5th

decades. In addition, an increasing body of work focuses on the role of inflammation and increased oxidative stress during aging. Our group previously showed that curcumin, a polyphenol component of turmeric with antioxidant and anti-inflammatory properties, delays cognitive decline in middle-aged (MA) macaques, as an early intervention. Here, we used three-dimensional reconstructions from serial section electron microscopy to analyze the density and morphological changes of axospinous synapses on layer 3 (L3) pyramidal neurons in area 46 of the DLPFC in rhesus monkeys, at different stages across their lifespan (young: 6-12 y.o.; MA: 13-20 y.o.; aged:21-28 y.o.). We aim to reveal ultrastructural alterations at early stages of the aging process and potential effects of the experimental treatment with curcumin in the MA cohort. Our results show that synapse loss and an increase in the size of presynaptic boutons in L3 of area 46 of the DLPFC, are present in MA. We also found that curcumin-treated monkeys maintain a better size correlation between pre- and postsynaptic components, including size of presynaptic mitochondria, than untreated middle-aged control and aged groups.We hypothesize that curcumin exerts a neuroprotective effect that might be related to its anti-inflammatory and antioxidant properties and preserves the structure of synapses in the MA cohort. Presynaptic mitochondria seem to be particularly benefiting from curcumin's antioxidative effects. By preventing morphological changes to mitochondria, induced in part by the build-up of oxidative stress during aging, curcumin may help mitochondria maintain their essential role in keeping up with metabolic demands during cognitive tasks. Altogether, curcumin may play an indirect role in maintaining synaptic efficacy, thereby helping to prevent the cognitive decline observed in middle-aged monkeys. A better understanding of the mechanism of action of curcumin in the brain is necessary to consider it as a nutraceutical supplement in early interventions to prevent age-related cognitive impairment.

Disclosures: C. Freire-Cobo: None. **M. Medalla:** None. **M. Varghese:** None. **J.I. Luebke:** None. **P.R. Hof:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.08/C56

Topic: C.01. Brain Wellness and Aging

Support: ICMR JRF 3/1/3/JRF-2019/HRD-080

Title: Evaluation of effect of non-invasive multisensory 40 Hz stimulation on sleep alterations in β-amyloid oligomers induced rat model of AD

Authors: *J. SUSHEEL KUMAR[1], D. YOGANARASIMHA[3], B. M. KUTTY[4], S. SUBRAMANIAN[2];
[1]Neurochemistry, [2]Dept. of Neurochemistry, Natl. Inst. of Mental Hlth. and Neuro Sci. (NIMHANS), Bengaluru, India; [3]Dept. of Neurophysiol., Natl. Inst. of Mental Hlth. and

Neurosciences (NIMHANS), Bengaluru, India; [4]Dept. of Neurophysiol., Natl. Instit Ment Hlt & Neurosci (NIMHANS), Bangalore, India

Abstract: Sleep disturbances frequently occur at the early stages of Alzheimer's disease (AD) and manifest decades before cognitive symptoms appear. Beta-amyloid pathology, a hallmark of AD, occurs during preclinical stages and is bidirectionally linked to disrupted sleep patterns. While non-pharmacological therapies, such as 40 Hz multisensory stimulation, are gaining interest in AD treatment, their impact on sleep remains relatively underexplored. To investigate this, we developed a non-transgenic AD model by bilateral intraventricular (AP: -1.0 and ML: ±1.6 to bregma, and DV: -3.8mm) injection of oligomeric beta-amyloid$_{25\text{-}35}$ peptide fragments (80microgram/kg) in 6-8 months old female Sprague-Dawley rats. Stereotaxic surgery was performed to implant stainless steel electrodes (250micrometer) into the CA1 region of the hippocampus (AP: -3.3, ML: -2.5 to bregma, and DV: -2.4mm) and medial prefrontal cortex (AP: +3.2, ML: +0.6 to bregma and DV: -3.6mm), nuchal muscles for electromyogram (EMG), external canthus of the eyes for electrooculogram (EOG), and scalp electrodes for reference and ground. After three weeks, polysomnography recordings were performed for 6 hours from 10:00 AM to 4:00 PM using a 16-channel video-EEG system. Rats with beta-amyloid injection exhibited significant sleep alterations, characterized by increased wake time and reduced duration of slow wave sleep (SWS), particularly in the initial hour of recording, indicating difficulty initiating sleep, though REM sleep remained unaffected. Subsequently, the rats were exposed to multisensory 40 Hz stimulation in a custom-made chamber. During stimulation, the dark chamber was illuminated by a light-emitting diode programmed at 40 Hz (12.5ms light on and 12.5ms off, 55W), and speakers fitted above the chamber programmed to present a 10KHz tone of 60 decibels, switched on for 1ms during light on period once in every 25ms. The multisensory stimulation consisted of simultaneous presentation of the tones and flickering light one hour per day for seven consecutive days. Polysomnography recording following multisensory stimulation revealed reduced wake duration and increased SWS, notably in the initial recording hour, suggesting improved sleep initiation. The increased sleep propensity after 40 Hz stimulation could be due to the accumulation of endogenous somnogen adenosine and glymphatic system-dependent clearance of beta-amyloid, as suggested by recent reports.

Disclosures: J. Susheel kumar: None. **D. Yoganarasimha:** None. **B.M. Kutty:** None. **S. Subramanian:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.09/C57

Topic: C.01. Brain Wellness and Aging

Support: 5R01AG067836

Title: Selective and potent PDE11A small molecule inhibitors reduce catalytic activity and reverse age-related clustering of the enzyme

Authors: E. AMURRIO[1], J. PATEL[1], P. KARGBO[1], P. KIM[1], C. HOFFMAN[2], S. MAHMOOD[3], D. ROTELLA[3], ***M. KELLY**[1];
[1]Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Boston Col., Chestnut Hill, MA; [3]Montclair Univ., Montclair, NJ

Abstract: PDE11A is a little-studied enzyme that breaks down cAMP/cGMP and is enriched in a memory-related brain region called the ventral hippocampus (a.k.a. anterior hippocampus in primates). Previous studies determined that age-related increases in PDE11A expression occur in human, rat, and mouse hippocampus. Interestingly, this age-related increase in PDE11A protein ectopically accumulates in membrane/particulate biochemical fractions and filamentous structures termed “ghost axons” due, in part, to phosphorylation of serine 117 and 124. Importantly, these studies also showed that preventing or reversing these age-related increases in PDE11A protein expression is sufficient to rescue age-related cognitive decline of social associative memory. Hence, we are developing the first potent, selective, and brain-permeable PDE11A small molecule inhibitors for the treatment of age-related cognitive decline. Not only do our small molecule PDE11A inhibitors reduce both the cAMP- and cGMP-catalytic activity of the enzyme, they also reduce the aging-like accumulation of PDE11A protein in an in vitro model. Further, pilot data suggest that brain-penetrant PDE11A inhibitors reverse the accumulation of PDE11A protein in ghost axons in mouse. The dispersing effects of PDE11A inhibitors on PDE11A are not due to a reduction in pS117/pS124, so additional mechanisms are under investigation. Together, these studies suggest that orally-available and brain-penetrant PDE11A small molecule inhibitors are capable of reversing an age-related pathology.

Disclosures: E. Amurrio: None. **J. Patel:** None. **P. Kargbo:** None. **P. Kim:** None. **C. Hoffman:** None. **S. Mahmood:** None. **D. Rotella:** None. **M. Kelly:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.10/C58

Topic: C.01. Brain Wellness and Aging

Support: CONAHCyT grants No.252808
CONAHCyT grants No. 847273

Title: Cerebrolysin ameliorates age-induced dendritic spine degeneration in the hippocampus and prefrontal cortex in mice

Authors: *L. AGUILAR HERNÁNDEZ[1,2], G. FLORES[3];
[1]Inst. Politécnico Nacional, Puebla, Mexico; [2]Inst. de Fisiología, Benemérita Univ. Autónoma de Puebla, Puebla, Mexico; [3]Univ. Autonoma de Puebla / Inst. de Fisiologia, Puebla, Mexico

Abstract: Aging is a natural process in living beings characterized by the progressive decline in the physiology and morphology of their tissues. The impact of aging on the central nervous system generates a decline in cognitive functions which causes an increase in the prevalence of dementia and mild-cognitive impairments in old people. Structures of the limbic system such as hippocampus and amygdala, and their connections with cortical regions such as the entorhinal and prefrontal cortex are essential for the execution of cognitive processes. This intercommunication occurs between the neurons of each region mainly through excitatory synapses on the dendritic spines. These are structures with high plasticity that depends on factors such as stimulation, neurotrophic factors, oxidative stress, among others. In aging, the intracellular and extracellular environment in the brain reduces neuronal plastic capacity as oxidative stress, cellular damage, and inflammation increase. Studies show that the administration of anti-inflammatory and antioxidant substances can slow down morphological, functional, and behavioral declines. Cerebrolysin (CBL) is a complex of protein derivatives obtained from the enzymatic degradation of porcine brain tissue. Its components cross the blood-brain barrier, which allows its peripheral administration. Its effect on the brain is similar to the endogenous neurotrophic factors such as BDNF since it exerts pleiotropic effects of neurogenesis, protection, and cell survival. It has been shown that CBL can reduce neuronal and behavioral alterations caused by psychiatric disorders in different animal models. In our study, the effect of CBL was analyzed in rodents of different ages to evaluate the age-induced changes in dendritic spine and recognition memory. The treatment was applied 5 days a week for 8 weeks. Subsequently, the novel object recognition test was performed to evaluate long- and short-term memory. Golgi-cox staining was used to determine the density and population changes of dendritic spines in the hippocampus, prefrontal cortex, and amygdala. Our results show an overall reduction in dendritic spine density in the analyzed areas as well as an increase in stubby spines and a reduction in mushroom spines in older mice compared to juvenile mice. Recognition memory showed age-induced deterioration, especially in long-term memory. CBL treatment managed to attenuate these age-induced degenerative features mainly in the hippocampus and prefrontal cortex. Furthermore, we observed an improvement in locomotor activity and recognition memory in old mice treated with CBL compared to their control group.

Disclosures: L. Aguilar Hernández: None. **G. Flores:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.11/C59

Topic: C.01. Brain Wellness and Aging

Support: A&S Faculty Research Grant from University of Hartford

Title: Effects of age and sex on ketogenic diet-induced metabolic shift and brain inflammation in healthy and 3xTg-AD mice

Authors: *P. SACCHETTI[1], C. C. BUTERA[1], K. CHARLAND[2];
[1]Biol., Univ. of Hartford, West Hartford, CT; [2]Neurol., Univ. of Michigan, Ann Arbor, MI

Abstract: While millions of individuals worldwide cope with neurological disorders, few pharmaceutical treatments are available on the market to alleviate or cure such debilitating diseases. The identification of additional tools, pharmacological and non-pharmacological, to limit disease progression is of primary interest to society, especially if inexpensive and easy to implement. We and many others have demonstrated that dietary interventions can affect metabolism and gut microbiome and induce systemic changes that can affect brain energetics and health. Previously, we showed that the ketogenic diet (KD), a high-fat, low carbs, and low protein diet, can impact molecular pathways involved with inflammation and oxidative stress. In the current study, we used C57BL/6J healthy mice to examine the role of age, sex, and previous exposure to the diet on the rate of metabolic shift induced by the KD. Further, we assessed the impact of the KD and these variables on the inflammatory status of the brain in a murine model of Alzheimer's disease (3xTg-AD mice). Our results demonstrated that age had no significant effect on the ketosis profile, but sex and previous exposure to KD caused significant differences in the production of ketone bodies. In addition, age-dependent increases in inflammatory marker expression detected in the hippocampus of 3xTg-AD mice were reduced by KD administration, especially in female mice. Understanding how different variables affect the efficiency of ketone body metabolism will allow the implementation of better diet paradigms and maximize the impact of the KD on inflammation and other hallmarks of Alzheimer's disease.

Disclosures: P. Sacchetti: None. **C.C. Butera:** None. **K. Charland:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.12/C60

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01AG068168-01

Title: Mesenchymal stromal cell extracellular vesicles improve working memory and clearance of neurodegenerative proteins in middle-aged rhesus monkeys.

Authors: *E. MACKIE[1], H. XIN[2], D. L. ROSENE[1], M. MEDALLA[1], T. MOORE[1];
[1]Boston Univ. Sch. of Med., Boston, MA; [2]Neurol., Henry Ford Hlth. Systems, Detroit, MI

Abstract: Normal aging in primates is characterized by impairments in the domains of executive function, working and recognition memory that are thought to be driven by myelin pathology. Contributing to this pathology may be a decrease with age in the efficiency of cerebrospinal fluid (CSF) clearance of neurotoxic proteins. Recently, mesenchymal stromal cell extracellular vesicles (MSC-EVs) have been shown to ameliorate age-related changes and neurodegenerative disease pathology. Here, we used cognitive testing and longitudinal assessments of CSF levels of

biomarkers for neurodegeneration, to assess the effects of long-term MSC-EV administration in middle aged rhesus monkeys (n = 6, 3 females and 3 males, ages 17-24 years). Six monkeys, balanced by treatment, received intravenous infusions of either 4×10^{11} particles of MSC-EVs or saline vehicle biweekly for 18 months. Testing consisted of performance on the Delayed Non-Matching to Sample task (DNMS - measuring object recognition memory) and the Delayed Recognition Span Task Spatial (DRSTsp - measuring spatial working memory) before and after 18 months of treatment. One-way ANOVA revealed that treated monkeys performed at a significantly higher level on the DRSTsp at re-testing relative to their baseline performance ($p = 0.0093$) whereas monkeys receiving vehicle were either similar to baseline performance or had declined. Treated monkeys also made significantly fewer perseverative errors at re-testing (choosing the previously correct stimulus) (ANOVA, $p = 0.005$) and made significantly fewer of these errors between baseline and retesting (ANOVA, $p = 0.01$). Assessments of neurodegenerative markers in CSF samples collected at the start of infusions then 6, 12, and 18 months during treatment were conducted using enzyme-linked immunosorbent assays for Amyloid Beta proteins, Aβ40, Aβ42, and axonal damage markers, neurofilament light and myelin basic protein. Preliminary analyses in this small cohort show that while protein levels were consistent over time in vehicle animals, treated animals showed an increase in levels of all measured proteins at 6 months which plateaued then decreased thereafter. Notably, at 12 months, EV treated monkeys had a significantly higher percent change from baseline in Aβ42 compared to vehicle treated monkeys (Student's t-test, $p = 0.047$). Aβ40 ($r = 0.86$, $p = 0.028$) and Aβ42 ($r = 0.95$, $p = 0.004$) levels at 12 months were also positively correlated with DRSTsp performance between baseline and retesting. This demonstrates that long-term MSC-EV treatment in aging rhesus monkeys improves working memory, which was correlated to enhancement of Aβ clearance.

Disclosures: **E. Mackie:** None. **H. Xin:** None. **D.L. Rosene:** None. **M. Medalla:** None. **T. Moore:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.13/C61

Topic: C.01. Brain Wellness and Aging

Support: CAPES
CNPq
UFCSPA

Title: Cannabidiol does not revert hippocampal neuroinflammation and memory impairment in aged obese rats

Authors: ***F. WICKERT**[1], J. JANTSCH[1], F. RODRIGUES[1], V. SILVA DIAS[1], C. PEREIRA MEDEIROS[1], G. FRAGA[1], Y. BITENCOURT[1], S. P. DE MATOS[2], M. GIOVENARDI[1], R. P.

GUEDES[1];
[1]Univ. Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil; [2]PPG, Univ. Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil

Abstract: Obesity is a complex chronic condition that is on the rise and raising significant concern. When it occurs alongside aging, it exacerbates the low-grade inflammatory process already present in elderly people. This inflammation can affect the central nervous system, leading to neuroinflammation and behavioral issues. It is crucial to understand how obesity affects the aging brain, as well as to find treatments that can reverse these effects. The endocannabinoid system plays a role in both inflammatory and neurological processes, suggesting that cannabidiol (CBD) might offer therapeutic benefits in this context. Our study aimed to determine whether CBD could mitigate the damage caused by obesity in aging. We used 38 male Wistar rats, 18 months old, and divided them into four groups: Control (CT), Control with CBD (CT+CBD), Cafeteria diet (CAF), and Cafeteria diet with CBD (CAF+CBD). Throughout the experiment, the groups were fed either a standard chow or a CAF. From the 9th week until euthanasia, the rats received either a vehicle (corn oil) or CBD (15 mg/kg/day) by gavage. To assess long-term memory, we conducted an object recognition test. After euthanasia, the hippocampus was removed to analyze the expression of proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), as well as endocannabinoid receptors CB1 and CB2 using qPCR. Animals on the cafeteria diet showed an increase in IL-6 expression, while TNFα expression remained unchanged across groups. CB1 and CB2 expression also increased in the CAF groups. Additionally, rats on the cafeteria diet performed worse on the object recognition memory test, indicating impaired memory. However, CBD treatment did not produce any significant effect on the memory test or gene expression of IL-6, TNFα and CBD receptors. The results from our study underscore the negative impact of obesity on the brain and confirm its damaging effects on memory and hippocampal neuroinflammation. Unfortunately, CBD treatment was unable to reverse the alterations caused by the cafeteria diet in these aging rats.This study was approved by the UFCSPA Institutional Animal Care and Use Committee under number 212/2022.

Disclosures: **F. Wickert:** None. **J. Jantsch:** None. **F. Rodrigues:** None. **V. Silva Dias:** None. **C. Pereira Medeiros:** None. **G. Fraga:** None. **Y. Bitencourt:** None. **S.P. de Matos:** None. **M. Giovenardi:** None. **R.P. Guedes:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.14/C62

Topic: C.01. Brain Wellness and Aging

Support: UFCSPA
CAPES

Title: Effect of caloric restriction on metabolic, behavioral, and redox profile parameters in adult and middle-aged male mice

Authors: *B. FRAGA[1], P. MOLZ[1], N. PERIN SCHMIDT[1], N. HILLER BONDARCZUK[2], P. SILVEIRA[1], M. HENRIQUE FERRI[1], J. MONTANEZ[1], D. DOS SANTOS[1], A. G. BARSCHAK[1], R. P. GUEDES[1], M. GIOVENARDI[1];
[1]Behavioral and metabolic Physiol., UFCSPA, Porto Alegre, Brazil; [2]UFCSPA, Porto Alegre, Brazil

Abstract: Calorie restriction (CR) has been widely discussed in the literature in recent decades due to its considerable health benefits, mitigating damage to health throughout the individual's life and preventing potential future losses. One aspect in which CR has proven to be highly effective is in mitigating cognitive and physical decline caused by the natural aging process across different species. Furthermore, CR can act as a positive approach to improving neural signaling, participating in synaptic transmission and brain plasticity. Therefore, our objective is to evaluate the effect of CR on metabolic and behavioral parameters as well as the redox profile, among adult and middle-aged male mice. Male C57BL/6 mice (N=40), approximately 21 days old were divided into four groups: adult control group (CONT-A, standard diet ad libitum for 13 weeks), adult restriction group (RD-A, 30% reduction of standard diet for 13 weeks), old control group (CONT-MA, standard diet ad libitum for 47 weeks), and old restrictive group (RD-MA, 30% reduction of standard diet for 47 weeks) with free access to water. At the end of the experiment, anxious behavior and recognition memory were evaluated by the light-dark and object recognition tests, respectively. Metabolic alterations were evaluated by weight, BMI, and Lee index, as well as glucose, total cholesterol, triglycerides serum levels. The redox profile in adipose and hepatic tissues was assessed by quantifying thiobarbituric acid reactive substances (TBARS) and sulfhydryls. Two-way ANOVA was used to perform statistical analysis. Our findings showed that in relation to metabolic parameters, RD-MA animals had significantly lower weights and weight gain compared to the CONT-MA animals. In addition, RD-MA animals had significantly lower weight gain, Lee index, and BMI values compared to RD-A animals. Additionally, RD-A animals presented a lower adipocytes number compared to RD-MA animals. CR did not produce significant effects on either biochemical or behavioral parameters. However, RD-MA animals presented lower sulfhydryls levels in the liver compared to CONT-MA and lower TBARS levels in adipose tissue compared to RD-A. In conclusion, CR shows promise in mitigating health damage throughout life and, consequently, preventing possible future damage. However, it was not able to influence the biochemical parameters or anxiety-like behavior and recognition memory impairments of the animals.

Disclosures: B. Fraga: None. **P. Molz:** None. **N. Perin Schmidt:** None. **N. Hiller Bondarczuk:** None. **P. Silveira:** None. **M. Henrique Ferri:** None. **J. Montanez:** None. **D. dos Santos:** None. **A.G. Barschak:** None. **R.P. Guedes:** None. **M. Giovenardi:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.15/C63

Topic: C.01. Brain Wellness and Aging

Support: UFCSPA
CAPES
CNPq

Title: Cannabidiol treatment mitigates anxiety-like behaviors and neuroinflammation in obese aged rats

Authors: *J. JANTSCH, F. RODRIGUES, F. WICKERT, V. SILVA DIAS, C. PEREIRA MEDEIROS, G. FRAGA, S. P. DE MATOS, Y. BITENCOURT, M. GIOVENARDI, R. P. GUEDES;
UFCSPA, Porto Alegre, Brazil

Abstract: Aging and obesity induce a chronic inflammatory process that can affect the central nervous system, leading to neuroinflammation, behavioral changes, and predisposition to neurodegeneration. There is a need to clarify the molecular mechanisms by which obesity affects the aged brain, as well as treatments that mitigate these consequences. One molecule that has been explored for its promising neuroprotective potential is cannabidiol (CBD). Our research group has already demonstrated that CBD treatment reverses behavioral and neuroinflammatory damage in the offspring of obese mothers. Therefore, our objective is to investigate whether CBD has the potential to be a strategy that reduces the central consequences of obesity in aged animals. 18-month-old (n=38) male Wistar rats were divided into 4 groups: Control (CT), CT+CBD, cafeteria diet (CAF), and CAF+CBD. The groups received either a chow diet or a cafeteria diet for 8 weeks and began receiving vehicle (corn oil) or CBD from the 9th week until euthanasia at the end of the 11th week. The animals received CBD orally at 15 mg/kg/day. As expected, the CAF groups showed increased body weight at the end of the experiment and visceral fat accumulation, with no effect of CBD. The open field test was conducted at the end of the 10th week, and the CAF+CBD group spent more time in the center and traveled a greater distance in the center compared to the CAF group. The CAF group had more freezing episodes compared to all other groups, including the CAF+CBD group. These data indicate that CBD may be an interesting agent for alleviating anxiety-like behaviors in animals with obesity. We also found that CAF consumption resulted in a reduction of the main endocannabinoids, anandamide and 2-arachidonoylglycerol, in the prefrontal cortex of the animals, with no effect of treatment. We observed an increase in CB1 receptor transcripts and a decrease in CB2 receptor transcripts in the obese animals in the prefrontal cortex, with no effect of CBD treatment. Interestingly, we found an increase in toll-like receptor 4 protein expression, as well as in IL-6 transcript levels in the cortex of CAF animals, but the CAF+CBD group was spared from these increases. Therefore, CBD plays an interesting anti-inflammatory role in the cortex of animals with obesity, but it does not appear to be through the regulation of endocannabinoid expression or modulation of CB1 and CB2 receptors. Our results indicate that the potential of CBD to treat the central effects of obesity during aging may be promising, but the continuation of our research is essential to decipher the exact protective mechanisms of this intervention. The study was approved by the UFCSPA IACUC (Nº 212/2022).

Disclosures: **J. Jantsch:** None. **F. Rodrigues:** None. **F. Wickert:** None. **V. Silva Dias:** None. **C. Pereira Medeiros:** None. **G. Fraga:** None. **S.P. de Matos:** None. **Y. Bitencourt:** None. **M. Giovenardi:** None. **R.P. Guedes:** None.

Poster

PSTR014: Aging: Therapeutic Strategies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.16/C64

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

Support: NIH Grant NS083704-05A1
NIH Grant P20 AG068077
NIH Grant P51 OD011107

Title: Phospho-thr181 tau vaccine efficacy studies in mouse and non-human primate models demonstrate robust immunogenicity, safety, target engagement, and reduced disease status

Authors: *J. P. HULSE[1], N. M. MAPHIS[2], S. DADRAS[1], J. PEABODY[1], M. WHELPLEY[3], M. KANDATH[1], C. M. WILSON[4], S. M. HOBSON[5], J. F. THOMPSON[5], K. VAN ROMPAY[6], D. BECKMAN[6], S. OTT[6], J. MORRISON[6], J. E. KNOEFEL[7], G. A. ROSENBERG[7], B. CHACKERIAN[1], K. BHASKAR[1];
[1]Mol. Genet. & Microbiology, Univ. of New Mexico, Albuquerque, NM; [2]Neurosciences, Univ. of New Mexico, Albuquerque, NM; [3]Univ. of New Mexico, Albuquerque, NM; [4]Radiology, Univ. of New Mexico, Albuquerque, NM; [5]Memory & Aging Ctr., Univ. of New Mexico, Albuquerque, NM; [6]Univ. of California Davis, Davis, CA; [7]Neurol., Univ. of New Mexico, Albuquerque, NM

Abstract: Pathological accumulation of microtubule-associated protein tau (MAPT or tau) is a hallmark of tauopathies, including Alzheimer’s disease. Several recent studies suggest pathological tau (pTau) correlates with neurodegeneration and cognitive decline. A rapid surge in tau-targeted clinical and pre-clinical trials indicates that decreasing the seed-competent pTau may help stabilize cognitive and behavioral symptoms in tauopathies. However, many current immunotherapy trials targeting pTau only show efficacy at high doses, making it challenging to scale up in more extensive trials or require potent adjuvants to have a reasonably sustained immune response. We performed a multi-species validation of our previously described (PMID: 31231552) Qβ virus-like particle-based vaccine technology targeting phosphorylated tau on threonine 181 (pT181-Qβ). The PS19 mouse model overexpressing human mutant P301S tau and the hTau mouse model expressing all six isoforms of human tau on a mouse tau deficient background were used to assess vaccine efficacy. Both the PS19 and hTau mice receiving a 2-dose series of pT181-Qβ showed cognitive rescue and reduced soluble and insoluble tau pathology compared to their Qβ sham vaccinated counterparts. pT181-Qβ vaccinated PS19 mice showed reduced cortical atrophy with smaller ventricle volume than the Qβ group. pT181-Qβ vaccination also reduced microgliosis and inflammasome protein expression in both the PS19

and hTau models. Six-year-old rhesus macaques received a 3-dose vaccine series with either pT181-Qβ or Qβ sham vaccine to assess immunogenicity and safety in a non-human primate model. pT181-Qβ vaccination elicited a long-lived high titer antibody response out to 49 weeks. Blood plasma samples of pT181-Qβ vaccinated primates showed an inverse correlation between tau antibody levels and circulating pT181 tau by Quanterix Simoa® assay. Peripheral blood mononuclear cells evaluated by flow-cytometry showed an elevation in B-cells without any increases in CD8+ cytotoxic T lymphocytes or natural killer cells. Other parameters of complete blood cell count and blood biochemistry panels were within normal limits. Post-necropsy brain tissue samples showed no abnormalities. We report that two different (PS19 and hTau) mouse models of tauopathy and rhesus macaques vaccinated with pT181-Qβ show robust immunogenicity, safety, efficacy, and target engagement with as little as two vaccine doses, thus paving the way for future Qβ-VLP based therapeutics for tauopathies.

Disclosures: J.P. Hulse: None. **N.M. Maphis:** None. **S. Dadras:** None. **J. Peabody:** None. **M. Whelpley:** None. **M. Kandath:** None. **C.M. Wilson:** None. **S.M. Hobson:** None. **J.F. Thompson:** None. **K. Van Rompay:** None. **D. Beckman:** None. **S. Ott:** None. **J. Morrison:** None. **J.E. Knoefel:** None. **G.A. Rosenberg:** None. **B. Chackerian:** None. **K. Bhaskar:** None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.01/C65

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

Title: Preliminary phase 2 trial of the novel first-in-class dual-functional medicine for treatment of Alzheimer's disease demonstrates promising results

Authors: *Y. WANG;
Guangzhou Magpie Pharmaceuticals, Co. LTD., Guangzhou, China

Abstract: Chronic brain hypoperfusion is a common clinical feature of Alzheimer's disease (AD), which increases tau phosphorylation (p-Tau) in the hippocampus and cortex, damages fast axonal transport, increases mTOR signaling, impairs learning-memory function, and promotes the formation of neurofibrillary tangles—a neuropathologic hallmark of AD. MN-08 is a novel first-in-class dual-functional second generation memantine nitrate that effectively antagonizes N-methyl-D-aspartic acid receptors (NMDAR) and concurrently releases nitric oxide (NO) to dilate cerebral blood vessels. In various animal models of AD and vascular dementia (VD), MN-08 was found to prevent neuronal and dendritic spine loss and attenuate cognitive deficits. MN-08 demonstrated remarkable therapeutic efficacy that surpassed that of both memantine and donepezil in animal models of AD and VD. In animal models of AD and a phase 2 clinical study, MN-08 significantly increased cerebral blood flow. Preliminary phase 2 clinical trial results showed that MN-08 increased cerebral blood flow more than 30% from baseline, which is

significantly greater than the 9.8% increase by the PDE5 inhibitor tadalafil as reported (Paul *et al.*, Alzheimer's Dement. 2022, 18: 2393-2402). Due to MN-08's superior therapeutic efficacy in animal models of AD and safety profile, a phase 2 clinical study in AD patients has been initiated. The progress of this phase 2 clinical trial will be reported.

Disclosures: Y. Wang: A. Employment/Salary (full or part-time):; Guangzhou Magpie Pharmaceuticals, Co. LTD.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Yuqiang Wang is a stock holder of Guangzhou Magpie Pharmaceuticals, Co. LTD. who is developing MN-08..

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.02/C66

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

Title: Rationale and Study Design for the Phase-3 Clinical Development Program of Masupirdine (SUVN-502), a Pure 5-HT_6 Receptor Antagonist, for the Treatment of Agitation in Patients with Dementia of Alzheimer's Type

Authors: *R. NIROGI, J. RAVULA, S. JETTA, V. GOYAL, V. BENADE, A. SHINDE, S. PANDEY, R. SUBRAMANIAN, M. RASHEED, A. MOHAMMED, P. JAYARAJAN, V. JASTI;
Suven Life Sci. Ltd., Hyderabad, India

Abstract: Agitation in Alzheimer's disease (AD) is one of the most disruptive aspects for both patients and caregivers and is linked to several negative health outcomes including a rapid cognitive decline, decreased quality of life, early admission to long-term care, and increased mortality. It affects up to 50% of patients with AD and becomes increasingly prevalent in the advanced stages of the disease. Masupirdine, earlier known as SUVN-502, is a pure, potent, and orally active serotonin-6 (5-HT_6) receptor antagonist. Post hoc analyses of the Phase-2 study of masupirdine in AD patients (NCT02580305) revealed potential benefits in reducing neuropsychiatric symptoms. Masupirdine notably improved agitation/aggression and related domains on the Neuropsychiatric Inventory (NPI-12) scale. Moreover, treatment with masupirdine attenuated aggressive behaviors in animal models of aggression like resident-intruder task and dominant-submissive assay. To confirm the effects of masupirdine on agitation/aggression, a Phase-3, double-blind, randomized, placebo-controlled, parallel group, global study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of masupirdine in patients with agitation in dementia of the Alzheimer's type (NCT05397639) has been initiated. About 375 participants from the USA and Europe will be recruited for the study. Participants (male or female of ≥50 years of age) who are independent living, having in-home services, or living in assisted living or nursing homes will be randomly assigned in a 1:1:1 ratio to receive

either 50 mg or 100 mg masupirdine or placebo for 12 weeks. Participants must meet the International Psychogeriatric Association (IPA) provisional consensus definition of agitation in cognitive disorders and have the diagnosis of Alzheimer's dementia. Cohen-Mansfield Agitation Inventory items score aligning to the IPA agitation criteria domains and the Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change score as related to agitation are the primary and key secondary endpoints, respectively. The study is currently recruiting participants.

Disclosures: R. Nirogi: A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **J. Ravula:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **S. Jetta:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **M. Rasheed:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **A. Mohammed:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **V. Jasti:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.03/C67

Topic: C.01. Brain Wellness and Aging

Title: A Phase I/IIa Basket Study to Access MP101's Effects on Biomarkers in the Cerebrospinal Fluid of Amyotrophic Lateral Sclerosis (ALS), Alzheimer's Disease (AD) and Secondary Progressive Multiple Sclerosis (SPMS) Participants

Authors: *J. G. GEISLER;
Mitochon Pharmaceuticals, Inc., Blue Bell, PA

Abstract: A Phase I/IIa Basket Study to Assess MP101's Effects on Biomarkers in the Cerebrospinal Fluid of Amyotrophic Lateral Sclerosis (ALS), Alzheimer's and Multiple Sclerosis (MS) Patients Mitochon was founded in 2014 with the mission to develop treatments for truly insidious diseases by direct modulation of the entire mitochondrial physiology using micro-doses of protonophores (uncouplers). Pharmacology has possible applications to a legion of diseases of neurodegeneration, autoimmune, neuromuscular, developmental and trauma, due to a common thread of mitochondrial dysfunction. All appear to be rooted in an energy crisis of lower ATP, high ROS production, and calcium overload. Mitochon's lead compound, MP101's,

mechanism of action (MOA) is based upon biophysics. The drug is a weak acid, oral brain penetrant small molecule, wide tissue distribution, drawn to the only organelle, out of ALL the organelles with a pH basic environment, the mitochondrial matrix. Once at the mitochondria, MP101 crosses through the outer and inner membrane, and into the mitochondrial matrix to deliver a proton (H^+). This non-genomic event changes the membrane potential, electron transport chain accelerates, thereby shutting down *overt* free radical production and simultaneously closes the voltage gated Mitochondrial calcium uniporter (Mcu), lowering calcium levels and preventing the opening of the mPTP (irreversible) that leads to imminent cell death. Interestingly, this non-genomic effect at lowering damage, cascades into genomic remodeling and mitophagy by lowering mTOR, but promoting repair by induction of *endogenous* BDNF production, involved in cognition and neural growth. In an attempt to demonstrate that many indications have a common issue rooted in mitochondrial dysfunction and MP101 may resolve this problem, Mitochon is conducting a "basket study" such that three seemingly different indications will be treated as one. ALS, Alzheimer's and Multiple Sclerosis participants will be enrolled at a CRU in Europe for ~15 nights, with CSF taken on Day 0, and Day 15, after 14 consecutive days of a fixed dose treatment of MP101 once-per-day oral administration. Safety and tolerability are the primary goals, with secondary goal to demonstrate biomarker changes in the CSF of pathways involved in free radical production, anti-oxidants, cytokines, apoptosis, repair, damage and mitophagy. If these pathways are significantly changed after 14-days of MP101 treatment, then there is high merit to exploring functional benefits in longer term studies.**Additional Information: www.mitochonpharma.com**

Disclosures: J.G. Geisler: A. Employment/Salary (full or part-time):; Mitochon Pharmaceuticals/Founder, CSO, FTE.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.04/C68

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

Support: NC Biotech grant 2023-FLG-0031
NSF grant CAREER BIO-1846408
NIH ADRC REC Scholarship
US Army W911NF-14-2-0087

Title: Mechanistic links to AMPK/SIRT1-related autophagic activation underlying synaptic resilience for molecular insights into treating dementia-related synaptopathy

Authors: K. A. ADAMS[1], K. RENTSCHLER[2], T. A. SUHAGIA[3], N. J. DEYONKER[4], Y. TANG[5], K. G. FARIZATTO[6], M. PAIT[7], M. GIANG[1], M. GREENE[8], R. HICKS[8], A. ACKERLEY[1], M. FITZGERALD[5], **M. F. ALMEIDA**[9], *B. BAHR[8];

[1]Univ. of North Carolina at Pembroke, Pembroke, NC; [2]U.S. EPA, Research Triangle Park, NC; [3]Univ. Of Memphis, Univ. of Memphis, Memphis, TN; [4]Chem., Univ. of Memphis, Memphis, TN; [5]Duke Univ., Durham, NC; [6]Neurosci. Ctr., Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [7]Wake Forrest Univ., Winston-Salem, NC; [8]Univ. of North Carolina, Pembroke, Pembroke, NC; [9]McAllister Heart Instituion, Univ. of North Carolina Chapel Hill, Chapel Hill, NC

Abstract: The progressive, fatal neurodegenerative disorder named Alzheimer's disease (AD) is the most prevalent form of age-related dementia and characterized by the buildup of corrupted protein structures and aggregates. Levels of misfolded proteins have been associated with cortical atrophy, especially in the medial temporal lobe, hippocampus, and entorhinal cortex. The protein accumulation pathology has been linked to disruption of the autophagy-lysosomal pathway (Wang et al. 2018 Curr Opin Neurobiol 48:52; Almeida et al. 2023 Ageing Res Rev 93:102162), and recent multi-omics studies revealed AD-related dysregulation of autophagic/lysosomal components and intracellular trafficking (Eteleeb et al. 2024 PLoS Biol e3002607). We have shown that different polyphenol-type compounds upregulate/promote lysosomal enzyme maturation, leading to enhanced protein clearance trafficking in models of AD and mild cognitive impairment (Viswanathan et al. 2012 ACS Med Chem Lett 3:920; Hwang et al. 2019 Internatl J Mol Sci 20:4432). Our multidisciplinary work found the peptidyl compound Z-FA-DMK to have the highest docking energy score among 15 tested at the active site of the lysosomal hydrolase cathepsin B (CatB), perhaps explaining the compound's neuroprotective modulation of CatB. Potent CatB inhibitors exhibited lowest energy scores. In organotypic hippocampal slice cultures, Z-FA-DMK elevated levels of p-AMPKα and SIRT1, and pathway blocking experiments suggest AMPK/SIRT1 involvement in beclin-1/VPS34-mediated autophagic activation. A strong correlation between the mature, single-chain 254-residue CatB-30 and enhanced SIRT1 and beclin-1 levels was found, and these biomarkers have crucial roles in initiating autophagy and facilitating autophagosome formation. Z-FA-DMK also enhanced LC3-I to LC3-II conversion and reduced p62/SQSTM1 levels, suggesting the absence of autophagosome accumulation. Chemoproteomics and target discovery techniques were utilized in an animal model of MCI. Early analyses point to significant expression increases in components of protein clearance pathways and proteins associated with trafficking for axonogenesis and synaptic dynamics (PSB6, NEDD8, Rab-10, VAT-1, CAMKV; p=0.035-0.0008). Validation steps involve immunoblot measures. Proteasome inhibition in hippocampal tissue treated with Z-FA-DMK resulted in lower SIRT1 levels but not beclin-1 or LC3-II levels, indicating that CatB-30 may have dual roles in modulating autophagic flux. Taken together, these results suggest that positive modulation of the autophagy-lysosomal pathway is important for the maintenance of axonal and synaptic integrity.

Disclosures: K.A. Adams: None. **K. Rentschler:** None. **T.A. Suhagia:** None. **N.J. DeYonker:** None. **Y. Tang:** None. **K.G. Farizatto:** None. **M. Pait:** None. **M. Giang:** None. **M. Greene:** None. **R. Hicks:** None. **A. Ackerley:** None. **M. Fitzgerald:** None. **M.F. Almeida:** None. **B. Bahr:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.05/Web Only

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

Title: A novel inhibitor of CIP2A against alzheimer's disease: an in-silico approach

Authors: *G. CHOUDHARY[1], A. GHOSH[2], H. SIDDIQUI[3], H. KAUR[4], A. PRAKASH[1], B. MEDHI[1];
[1]Pharmacol., PGIMER, Chandigarh, India; [2]Chandigarh Univ., Chandigarh, India; [3]Panjab Univ., Chandigarh, India; [4]Immunopathology, PGIMER, Chandigarh, India

Abstract: Background: Alzheimer's disease (AD) is the most common form of dementia in elderly individuals, characterized by cognitive decline and memory impairment. With a high fatality rate, effective therapies are urgently needed. Two critical factors in selecting a therapy for AD are its precision in targeting the intended site and its ability to cross the blood-brain barrier (BBB). In this study, we focused on targeting the CIP2A protein, implicated in AD pathology, using a virtual screening in silico approach based on structural data. **Materials and Methods:** We employed a virtual screening method to identify potential molecules that could target the CIP2A protein. Structural data of CIP2A were used to create a ligand database for evaluating molecular fit. Additionally, we conducted ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) assessments and molecular dynamics (MD) simulations to assess the viability of candidate molecules. **Discussion:** Our extensive computer-based studies identified four promising compounds: LAS 52465210, BDH 34002080, LAS 58002491, and LAS 54566256. These molecules demonstrated the potential to block interactions involving the CIP2A protein. By increasing PP2A levels and reducing Tau protein clustering, these compounds have the potential to mitigate neurofibrillary tangles, synaptic issues, and neuron damage associated with AD pathogenesis. **Conclusion:** In conclusion, our study presents a novel approach to identifying potential therapies for AD targeting the CIP2A protein. Through virtual screening, ADMET assessments, and MD simulations, we identified four promising compounds that warrant further investigation for their therapeutic potential in preventing cognitive decline and memory issues associated with AD. These findings contribute to the ongoing efforts to develop effective treatments for this devastating neurodegenerative disease.

Disclosures: G. Choudhary: None. **A. Ghosh:** None. **H. Siddiqui:** None. **H. Kaur:** None. **A. Prakash:** None. **B. Medhi:** None.

Poster

PSTR015: Alzheimer’s Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.06/C69

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

Support: U19 NS110456

Title: Comparative binding properties of tau PET tracers JSS20-183A, PI-2620 and T807 in postmortem Alzheimer's disease, progressive supranuclear palsy and corticobasal degeneration brains and in tau p301s mouse model.

Authors: *D. SATURNINO GUARINO[1], J. STEHOUWER[2], E. GALLAGHER[3], H. XU[1], E. B. LEE[4], J. ROBINSON[1], V. M. LEE[5], N. VASDEV[6], C. A. MATHIS[2], R. H. MACH[7]; [1]Univ. of Pennsylvania, Philadelphia, PA; [2]Radiology, Univ. of Pittsburgh, Pittsburgh, PA; [3]Neurosci. Grad. Group, Univ. of Pennsylvania, Philadelphia, PA; [4]Dept. of Pathology and Lab. Med., Univ. of Pennsylvania, Philadelphia, PA; [5]Dept Pathol & Lab. Med., Univ. Pennsylvania Sch. Med., Philadelphia, PA; [6]Univ. of Toronto, Toronto, ON, Canada; [7]Univ. of Pennsylvania Neurosci. Grad. Group, Wallingford, PA

Abstract: Purpose: The aim of this study was to compare the binding properties of three tau positron emission tomography tracers- JSS20-183A, PI-2620, T807 (also known as AV1451; flortaucipir ,Tauvid)- in a head-to-head comparison in the same human and mouse brain tissue in order to understand the binding profile of each radiotracer. **Methods:** We characterized the binding of the tau tracers in formalin fixed paraffin embedded (FFPE) human post-mortem brain tissue and in the 4RTau P301S mouse model sections using *in vitro* real time autoradiography with tritium-labelled radiotracers in conjunction with phospho-tau specific immuno-histochemistry. Binding assays were performed to compare the regional distribution of the tau ligands in AD, PSP, CBD cases in frontal and parietal cortex. Competition binding assays between PI-2620 and T807 were also included using autoradiography. **Results:** [^{3}H]JSS20-183A, [^{3}H]PI-2620, [^{3}H]T807 autoradiography of FFPE sections from 2 AD cases showed similar regional binding for the three tracers, with [^{3}H]T807 demonstrating the highest specific binding of the three in AD brain. However, results from two CBD and two PSP cases showed high binding of [^{3}H]JSS20-183A and very low specific binding of [^{3}H]PI-2620 and [^{3}H]T807. The binding properties of the three tau tracers in P301S mouse brain, a mouse model of 4R tauopathies, recapitulated the results in the human brain samples of the 4R tauopathies. Blocking studies of [^{3}H]JSS20-183A was performed using ARG competition with unlabeled JSS20-183A, PI-2620 and T807 (1 uM) in cortical areas. The % inhibition was: 1) AD (60-70% by JSS20-183A, 40-50% by PI-2620; 30-40% by T807); 2) CBD (77% by JSS20-183A, 60% by PI-2620; 50% by T807); and PSP (60% by JSS20-183A, no displacement by PI-2620; 10% by T807). **Conclusions:** These results demonstrate the different binding properties among the second-generation tau PET tracers, which may assist in further understanding of tau heterogeneity in AD versus non-AD tauopathies. The data supports the use of [^{18}F]JSS20-183A in PET imaging studies of the 4R tauopathies.

Disclosures: D. Saturnino Guarino: None. **J. Stehouwer:** None. **E. Gallagher:** None. **H. Xu:** None. **E.B. Lee:** None. **J. Robinson:** None. **V.M. Lee:** None. **N. Vasdev:** None. **C.A. Mathis:** None. **R.H. Mach:** None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.07/C70

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

Support: La Dassault Systemes Fondation grant DSF/10753
Indian Space Research Organization grant ISRO/RAC-S/IIT(BHU)/10
Dept. of Science & Technology-India Ihub-Ntihac grant 1096

Title: Neuroanatomically-specific drugs for amyloid clearance therapy in sub-types of Alzheimer's disease: Correlation with developmental origins of cerebral regions.

Authors: *P. K. ROY[1], A. BHATTACHARJEE[2];
[1]Life Sci., Shiv Nadar Univ., Greater Noida (Delhi NCR), India; [2]Biomed. Engg., Indian Inst. of Technol. (BHU),, Varanasi, India

Abstract: INTRODUCTION:.Cerebrum has three successive developmental phylogenic regions: 1) Paleopallium - as uncus/uncinate node, 2) Archipallium - limbic area as orbitofrontal node, 3) Neopallium - cortical mantle as parietal node. Using MRI-DTI, we earlier showed that fiber tracts form transport scaffolds for tumors and migratory entities [PMID 31264025]. We will use MRI-DTI to demarcate the amyloid migration paths in those three regions. Using systems biology approach, we had earlier found that the amyloid efflux receptors (that enables brain amyloid's clearance via blood-liver-fecal route) are Bile pump receptor (BP-R), Phosphodiesterase receptor (PD-R) and Pregnane-x receptor (PX-R); these clearance receptors are respectively associated with genes ABCB11, ABCA1 and MDR1, and are respectively activated by drugs Metformin, Cilostazol, Rifampin [PMID 36510663]. .**METHODS:**.We analyze 3T MRI scans from our earlier study and AD neuroimaging initiative and reconstruct the nerve tracts in the above paleopallial, archipallial and neopallial nodes. Via DTI, we assess neuronal integrity in these nodes in AD and controls (n=10/10). From Allen brain atlas microarray analysis we map gene expression of efflux genes ABCB11, ABCA1, MDR1 across 3D brain tissue. We also perform clinical trial analysis of the three amyloid clearance drugs (metformin, cilostazol, rifampin) on AD subjects (n=20, 36, 40) where clinical cognitive enhancement is observed ($p<0.05$). . **RESULTS:**.Tractography of those paleopallium, archipallium and neopallium nodes respectively furnishes three centrifugal tracts for amyloid spread: 1) Thalamocortical radiation, 2) Frontooccipital fasciculus 3) Superior longitudinal bundle. These three sectorial phases correspond to the three histological Braak stages A-B-C of AD progression, and these three pallium phases correlate with the three neuroanatomical AD subtypes: frontal, temporal, parietal variants. We find that in AD, the downregulation of the genes ABCB11, ABCA1 and MDR1 (by 64%, 165%, 111%) only occur respectively in paleopallium, archipallium or neopallium nodes, and not in the other two pallium nodes. In AD patients we found that metformin, cilostazol, rifampin activated respectively the paleo-, archi- or neopallium nodes and not the other two pallium nodes (as we noted by MRI/PET). DTI showed that pretreatment AD patients have considerable neuronal integrity deficit in the nodes

($p<0.01$)..**CONCLUSION:**.Our developmental phylogenic analysis shows that AD is a polysyndrome and different amyloid-clearance drugs are efficacious according to the neuroanatomical pallium involved, thus enabling personalized therapeutics.

Disclosures: P.K. Roy: None. **A. Bhattacharjee:** None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.08/C71

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

Title: Design and development of N-(4-phenylthiazol-2-yl)-2-(piperazin-1-yl) acetamide conjugates as a multifunctional moeity for the treatment of Alzheimer's disease

Authors: *A. SINGH, S. SHRIVASTAVA;
Pharmaceut. Engin. and Technol., Indian Inst. of Technol. (Banaras Hindu University), Varanasi, India

Abstract: Design and development of N-(4-phenylthiazol-2-yl)-2-(piperazin-1-yl)acetamide conjugates as a multifunctional moiety for the treatment of Alzheimer's disease
*Abhinav Singh, Sushant Kumar Shrivastava**Pharmaceutical Chemistry Research Laboratory, Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University) Varanasi-221005*
AbstractArtificial Intelligence is a versatile tool for designing drug candidates and plays a crucial role in drug discovery and development. In this study, Therapeutic Target Database (TTD) was utilized for developing in house library of piperazine-type molecules with the help of similarity search tool. Further, in house library of 234 compounds containing piperazine moiety were screened using Virtual Screening Workflow module of Schrodinger where 5 Hits were showing utmost affinity towards the enzyme targets. Later, N-(4-phenylthiazol-2-yl)-2-(piperazin-1-yl)acetamide multifunctional pharmacophore was developed using molecular hybridization approaches and further synthesized and characterized using various spectroscopic techniques. Initially, the preliminary efficacy of designed molecules was evaluated against *ee*AChE and DPPH-based free radical scavenging assay. Compounds 61 (54.24 ± 0.010 %) and 76 (51.26 ± 0.012 %) showed excellent percentage inhibition compared to control in the DPPH-based free radical scavenging assay demonstrating its potency against oxidative stress. In the Ellman assay of cholinesterase inhibition, compound **61 (42.25 ± 0.032 %)** and **76 (41.24 ± 0.036 %)** displayed significant inhibition only. Propidium Iodide (PI) displacement, PAMPA Assay, *in vivo* acute toxicity and Y-maze test will be performed to check the PAS-binding affinity, BBB permeability, optimum dose and short-term memory dysfunction. Eventually, *ex-vivo* experiments will be carried out using brain tissue homogenate for neuronal and biochemical estimation. **References:**1.Sharma, P., Tripathi, A., Tripathi, P.N., Singh, S.S., Singh, S.P. and

Shrivastava, S.K., 2019. Novel molecular hybrids of n-benzylpiperidine and 1, 3, 4-oxadiazole as multitargeted therapeutics to treat alzheimer's disease. *ACS chemical neuroscience*, *10*(10), pp.4361-4384.2.Tripathi, A., Choubey, P.K., Sharma, P., Seth, A., Tripathi, P.N., Tripathi, M.K., Prajapati, S.K., Krishnamurthy, S. and Shrivastava, S.K., 2019. Design and development of molecular hybrids of 2-pyridylpiperazine and 5-phenyl-1, 3, 4-oxadiazoles as potential multifunctional agents to treat Alzheimer's disease. *European journal of medicinal chemistry*, *183*, p.111707.

Disclosures: A. Singh: None. **S. Shrivastava:** None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.09/C72

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

Title: An In Silico study aimed at the screening of potential therapeutic candidates derived from Psychedelics for Alzheimer's Disease

Authors: *A. TRISAL[1], H. CHOUDHARY[2], M. ILHAM[3], N. PAUL[2], S. NAG[2], C. ARCOT[2], M. BHARTI[4], J. SHIVHARE[2];
[1]Jamia Millia Islamia, New Delhi, India; [2]ITM Univ., Gwalior, India; [3]Universitas Andalas, Kota Padang, Indonesia; [4]Patna Univ., Patna, India

Abstract: Although psychedelics have historically been used for recreational and spiritual reasons, advances in psychotherapy have brought attention to their potential as therapeutic tools. The management of neurodegenerative diseases, especially dementia, may benefit from these discoveries, but their implications have not yet been thoroughly investigated. We propose that by affecting important protein targets linked to AD pathology, psychedelics (psilocybin, LSD, and DMT) can modulate and shield against the disease's pathology. These targets include β-Secretase 1 (BACE1) (PDB ID: 6XDS), Triggering Receptor Expressed on Myeloid cells 2 (TREM2) (PDB ID: 8FO7), Leucine-Rich Repeat Kinase 2 (LRRK2) (AlphaFold model accession: AF-V8NH92-F1-model_v4), and Amyloid Precursor Protein (APP) (AlphaFold model accession: AF-P05067-F1-model_v4). A cheminformatics software package was used to create a ligand library based on LSD. During the first in-silico ADME screening, major compounds with promising drug-like characteristics were found. After additional assessment of the resultant library with SwissADME, a final list of the top candidates with acceptable pharmacokinetics and ligand efficiency was obtained. Using Autodock Vina, molecular docking simulations were performed on the top ligand candidates against BACE1 and TREM2 and showed advantageous binding energies between -7.0 and -9.0 kcal/mol. Detailed insights into the possible binding modes were obtained through the use of Discovery Studio Visualizer for ligand-protein interaction analysis. The promising ligands exhibited a mix of pi-stacking, hydrophobic, and

hydrogen bonding interactions with the target proteins, which may have contributed to the favorable predicted binding energies of the compounds. Using molecular dynamics (MD) simulations, a portion of the top-ranked ligands were chosen for additional study to assess dynamics and stability of the ligand-protein complexes. Retrosynthetic analysis was carried out in order to develop viable synthesis routes appropriate for wet-lab experiments. The most promising candidates' retrosynthetic analysis revealed workable synthesis routes for additional wet-lab testing. These results open the door to the creation of cutting-edge Alzheimer's disease treatment approaches.

Disclosures: A. Trisal: None. **H. Choudhary:** None. **M. Ilham:** None. **N. Paul:** None. **S. Nag:** None. **C. Arcot:** None. **M. Bharti:** None. **J. Shivhare:** None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.10/C73

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

Support: NIH grant R01AG057767
NIH grant R01AG061937
Smith Alzheimer's Center
Kenneth Stark Endowment

Title: Lifespan of male and female APP/PS1 and $APP^{NL\text{-}F/NL\text{-}F}$mouse models of Alzheimer's disease

Authors: H. ROBERTS[1], Y. FANG[1], K. QUINN[1], T. HILL[1], M. R. PECK[1], A. BARTKE[2], *K. N. HASCUP[1], E. R. HASCUP[1];
[1]Dale and Deborah Smith Ctr. for Alzheimer's Res. and Treatment, Southern Illinois Univ. Sch. of Med., Springfield, IL; [2]Intrnl. Med., Southern Illinois Univ. Sch. of Med., Springfield, IL

Abstract: Alzheimer's disease (AD) disproportionately affects women, yet most preclinical research studies are male-centric. Recent data support biological and pathological sexual dimorphism in AD progression. To investigate if this dimorphism might also contribute to longevity differences, we performed a primarily retrospective lifespan comparison of APP/PS1 and $APP^{NL\text{-}F/NL\text{-}F}$ AD mouse models to their shared genetic background control (C57BL/6). Male and female APP/PS1, $APP^{NL\text{-}F/NL\text{-}F}$, and C57BL/6 mice born in our breeding colony were monitored from birth until date of natural death or at veterinarian's request for moribund/health issues. Age was recorded by number of days alive. Kaplan-Meier survival distributions of percent survival probability were performed using a Log-rank (Mantel-Cox) test. Minimal and maximal days alive were calculated by averaging age across the youngest and oldest 20% survived, respectively. We used unpaired t-tests for within genotype sex for maximal and

minimal days alive and a one-way ANOVA with a Tukey's post hoc test to compare genotypes. Significance was determined as $p<0.05$. Survival distributions indicate significant difference between males and females for each genotype, and longer survival of males than females for the C57BL/6 and APP/PS1 groups. Same sex genotype comparisons support decreased survival distributions in APP/PS1 mice, but increased in $APP^{NL-F/NL-F}$ mice for both sexes. There was no significant difference between C57BL/6 and APP/PS1 minimal days alive, however, these groups had significantly shorter minimal days alive compared to sex-matched $APP^{NL-F/NL-F}$. APP/PS1 mice had significantly decreased maximal days alive compared to both C57BL/6 and $APP^{NL-F/NL-F}$ for both sexes. There was no difference in sex-matched C57BL/6 and $APP^{NL-F/NL-F}$ maximal days alive. The sex differences observed in this study may be due to the APP/PS1 transgenic strain overexpressing APP and PSEN1 genes, leading to accelerated disease onset and severity (similar to early-onset AD in humans) when compared to the $APP^{NL-F/NL-F}$ knock-in model that is representative of sporadic AD occurring later in life. Additionally, data support that upregulating PSEN1 may be responsible for the early mortality and pathology observed in APP/PS1 mice. Furthermore, previous male-centric AD preclinical research may have contributed to the poor translatable success of mouse to human studies, underlining the importance of including both sexes in animal research. This lifespan study supports sexual and genotype dimorphic lifespan and healthspan in AD, warranting the need to examine mechanisms and potential treatments in both sexes.

Disclosures: H. Roberts: None. **Y. Fang:** None. **K. Quinn:** None. **T. Hill:** None. **M.R. Peck:** None. **A. Bartke:** None. **K.N. Hascup:** None. **E.R. Hascup:** None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.11/C74

Topic: C.01. Brain Wellness and Aging

Support: CONAHCyT Grant 288396
CONAHCyT Grant 1-S-42600
CONAHCyT Grant 163235 INFR-2011-01

Title: Effect of a fiber-enriched diet on cognition and amyloidosis in female APP/PS1 model of Alzheimer´s disease

Authors: *D. CUERVO-ZANATTA[1], J. HERNANDEZ[2], J. GARCÍA-MENA[3], C. PEREZ-CRUZ[4];
[1]Engin., Anáhuac Univ., Córdoba, Mexico; [2]Fisiologia de la Nutricion, Univ. Nacional Autónoma De México, Ciudad de Mexico, Mexico; [3]Genet. and Mol. Biol., Ctr. for Res. and Advanced Studies of the Natl. Polytechnic Inst., Ciudad de México, Mexico; [4]CINVESTAV, Mexico City, Mexico

Abstract: Alzheimer's disease (AD) is an age-related condition characterized by cognitive impairment and β-amyloid burden in brain, which seems to be higher in females regarding males. Recent studies have suggested cognitive improvements and decreases in hippocampal number of amyloid plaques in APP/PS1 (a transgenic (Tg) mice model of AD) males due to soluble fiber intake. However, there is no sufficient data about the potential benefits of soluble fiber against cognitive deficits and amyloidosis in APP/PS1 females. Here, we show that intake of fructans-enriched food resulted in improved memory scores and lower levels of anxiety regarding control diet despite no plaque number decreases in brain. The benefits of fiber on memory, learning, and anxiety appear to depend on the integrity of the gut microbiota.

Disclosures: D. Cuervo-Zanatta: None. **J. Hernandez:** None. **J. García-Mena:** None. **C. Perez-Cruz:** None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

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Program #/Poster #: PSTR015.12/C75

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

Support: NIH Grant R21 AG072487
AFTD Postdoctoral Fellowship 2022-02

Title: Revamping Adrenergic Signaling Axis as a Potential Therapeutic Target Against Tau-Mediated Neurodegeneration

Authors: *S. JATI[1], D. E. MUNOZ-MAYORGA[2], X. CHEN[3], G. GHOSH[1], S. MAHATA[1]; [1]Univ. of California San Diego, San Diego, CA; [2]Univ. of California San Diego, La Jolla, CA., CA, ; [3]UCSD, La Jolla, CA.

Abstract: Tauopathy comprises a class of neurological disorders where Tau proteins undergo toxic post-translational modification and subsequent aggregation in neurons and glial cells. The alpha-adrenergic signaling axis includes a class of G-protein Coupled Receptors (GPCR), which bind with catecholamines (epinephrine; EPI and nor-epinephrine; Nor-EPI) and play a significant role in vasculature smooth muscle contraction and cardiac function. Despite its in-depth study in peripheral regulation, its role in cognition and neurotransmission is not clearly known. Several lines of evidence suggest the presence of augmented alpha-1 adrenergic receptor (ADRA1) agonists (autoantibodies against ADRA1) in the Alzheimer's Disease (AD) cortex. Although altered alpha-adrenergic receptor has been known to modulate the disease pathogenesis in AB-mouse models, there has been no such comprehensive study to explore the role of this receptor and its ligand (EPI and Nor-Epi) in tau-mediated neurodegeneration. My study found augmented EPI levels in cerebrospinal Fluid and pre-frontal cortex of both primary (CBD; Cortico Basal Degeneration) and secondary tauopathies (AD) and have emerged as a prominent feature in the

disease. A similar difference in EPI was also observed in a mouse model of tauopathy (PS19/hTau P301S) when compared to Wildtype. Interestingly, the Nor-EPI level change is insignificant between healthy and diseased patient CSF and frontal cortex. EPI treatment in AAV-hTau (P301S) transduced Organotypic slice culture (OTSC) from the hippocampus revealed a substantial increase in Tau hyperphosphorylation (Ser 396/404 and Ser 202) and aggregation. To my surprise, the transcriptomics analysis exhibited an elevated ADRA1 and downregulated alpha-2 adrenergic receptor (ADRA2) in the frontal cortex of hTau mice compared to Wildtype. In contrast, the level of Beta-adrenergic receptors remains unchanged. Similar ADRA1 and ADRA2 changes were observed in the Braak 6 stage AD patient frontal cortex and parahippocampal gyrus. Further, we administered ADRA1 agonist (Phenylephrine) and antagonist (Prazosin) in AAV-hTau, transduced OTSC, and observed increased and decreased Tau aggregation, respectively. Altogether, these data demonstrate EPI-alpha1 adrenergic signaling as a critical regulator of Tau-mediated neurodegeneration. Since neurodegeneration is the outcome of complex metabolic dysfunction and neuroinflammation, considering the multifaceted effect of EPI-alpha adrenergic signaling on metabolism and inflammation, this approach opens up a therapeutic avenue against the disease.

Disclosures: S. Jati: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.13/C76

Topic: C.08. Ischemia

Support: NIH R01 NS166199

Title: Spak-nkcc1 cascade inhibition restores the blood-brain barrier integrity and improves cerebral blood flow in a mouse model of vcid

Authors: M. SULTAN[1,2], M. HABIB[1,3], M. RAHMAN[1], S. KUNDU[1,3], I. JAHAN[1,3], I. MENDEZ[1], D. SUN[4], G. CAO[4], ***M. BHUIYAN**[1,3];
[1]The Univ. of Texas at El Paso, El Paso, TX; [2]Dept. of Neurol., LSU Hlth. Shreveport, Shreveport, LA; [3]Dept. of Neurol., LSU Hlth., Shreveport, LA; [4]Dept. of Neurol., Univ. of Pittsburgh Med. Sch., Pittsburgh, PA

Abstract: Background: Vascular contributions to cognitive impairment and dementia (VCID) is one of the leading causes of dementia, where microglial and astroglial activation, blood-brain barrier (BBB) breakdown, and chronic cerebral hypoperfusion (CCH) are the key features. However, the molecular and cellular mechanisms underlying VCID are not well understood. Activation of Na-K-Cl cotransport 1 (NKCC1) via its upstream regulatory kinase SPAK (the STE20/SPS1-related proline/alanine-rich kinase) causes intracellular Na^+ overload, hypertrophy,

and astrogliosis. In this study, we investigated whether pharmacological inhibition of the SPAK-NKCC1 cascade attenuates microglial activation, reactive astrogliosis and BBB breakdown, and improves cerebral blood flow (CBF) in a mouse model of VCID. **Methods**: VCID was mimicked in young adult male mice with bilateral carotid artery stenosis (BCAS). CBF was monitored by laser speckle imaging, and CCH-induced cognitive deficits were assessed using the Moris water maze and novel object recognition tests. A specific inhibitor of SPAK, ZT-1a, was administered (5 mg/kg, i.p) to inhibit SPAK-NKCC1 complex activity in BCAS mice. The expression of NKCC1, BBB proteins, angiogenesis markers, and demyelination were examined by immunofluorescence staining. **Results**: BCAS mice exhibited CCH, white matter lesions, and cognitive function deficits. Increased NKCC1 expression and phosphorylation were found in Iba^+ activated microglia and in $GFAP^+$ reactive astrocytes from the early (2 wk) to the later stages (8 wk) following BCAS. Reduced expression of BBB marker ZO-1 and Claudin-5 was noted in vessels marked by tomato lectin, alongside elevated levels of serum albumin in the brain parenchyma of BCAS mice, suggesting hypoperfusion-induced BBB leakage. Levels of angiogenesis markers were increased in BCAS mice compared to those in sham mice. Interestingly, treatment with ZT-1a in mice during the chronic stage (4-8 wks) post-BCAS induction attenuated BCAS-induced activation of microglia and astrocytes, BBB breakdown, and significantly improved CBF and axonal myelination. **Conclusion**: Our results suggest that the SPAK-NKCC1 cascade activates microglia and astrocytes and causes BBB breakdown and oligodendrocyte cell death. Delayed inhibition of the SPAK-NKCC1 complex has therapeutic potential for alleviating pathogenesis and promoting vascular integrity in VCID. *This research was supported by NIH R01 NS166199 Grant (M.I.H.B.).*

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Poster

PSTR015: Alzheimer's Disease and Related Dementias: Therapeutic Strategies and Biomarkers

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.14/C77

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH NINDS Grant R21NS121589

Title: Histological and Transcriptomic Insights into Vascular Changes in Moyamoya Disease

Authors: *T. CHIANG[1,3], S. HE[2,3], M. Y. CHENG[2,3], G. K. STEINBERG[2,3];
[2]Neurosurg., [1]Stanford Univ., Stanford, CA; [3]Stanford Stroke Ctr., Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Background: Moyamoya disease (MMD) is a rare progressive cerebrovascular disease that can lead to ischemic and hemorrhagic strokes. A main characteristic of MMD is the

thickening of the innermost layer (intima), leading to the narrowing of arteries that supply oxygen to the brain. However, the mechanism underlying this pathology is largely unknown. To address this, we investigated the histological characteristics of vessel samples from MMD patients and performed spatial transcriptomics. Specifically, we analyzed the principal cell types in the blood vessels - endothelial cells (EC) and vascular smooth muscle cells (VSMC), in M4 middle cerebral artery (MCA) and superior temporal artery (STA) samples. Methods: STA and/or MCA were collected during surgical bypass to treat MMD in patients or other vascular diseases (Control STA). MCA and STA samples were sectioned and stained for endothelial cells (CD31), vascular smooth muscle cells (αSMA), actin filaments (phalloidin), and nuclear staining (Hoechst33342). Sections were imaged with Zeiss laser scanning microscope (LSM800) and analyzed with ImageJ for quantification. An additional set of samples were processed for Nanostring Spatial Transcriptomics. Results: Immunohistochemistry staining for CD31 and α-SMA revealed marked differences in the intima and media layers between MMD and control samples. In the MMD STA, αSMA expression was found in both the media layer and the intima layer, in contrast to control STA where αSMA expression was mostly in the media. In addition, the morphology of VSMCs in MMD STA differed significantly; control STA mostly displayed a contractile phenotype with elongated, spindle-shaped cells, whereas MMD STA exhibited synthetic phenotype with shorter, cobblestone appearance. Furthermore, phalloidin staining, which highlights actin filaments, showed greater intensity in MMD STA and MCA. Quantification of intima layer thickness also showed a significant increased intima thickness in MMD STA. Spatial transcriptomes of these vessels have been processed to identify gene expression differences in these vessel layers in MMD. Conclusions: Our findings showed morphological differences in VSMCs in the MMD STA, indicating a shift towards synthetic phenotype associated with increased cellular proliferation and reduced contractility, which can contribute to the MMD pathology. The increased phalloidin staining in MMD vessels aligns with this synthetic phenotype, reflecting more robust cytoskeleton remodeling. Ongoing studies include analysis of transcriptome changes across different layers in MMD to identify key molecular changes driving these pathological features.

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Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.01/C78

Topic: C.03. Parkinson's Disease

Support: NIH, NeuroBioBank

Title: Effects of Parkinson's Disease on the Neuromuscular Junction of LRRK2 Transgenic Mouse

Authors: *P. KEEFE[1], K. BRAKE[1], K. DINOVO[2], M. BAJWA[3], I. MARTINEZ-PENA Y VALENZUELA[2];
[1]Chicago Col. of Osteo. Med., [2]Col. of Grad. Studies, Physiol., Midwestern Univ., Downers Grove, IL; [3]Univ. of Illinois, Champaign-Urbana, IL

Abstract: INTRODUCTION Parkinson's Disease (PD) stems from a loss of dopaminergic neurons within the Basal Ganglia. This loss induces symptoms of bradykinesia, "frozen" facial expression, propulsive/festinating gait, resting "pill-rolling" tremor, and others. While a central neurodegenerative disease, this characterization may limit consideration of possible peripheral disease manifestations. Because PD is foremost a movement disease, the neuromuscular junction (NMJ), the connection between muscular and nervous systems, represents a site worthy of study. In other movement disorders, degradation of Nicotinic Acetylcholine Receptor (nAChR) is well established and contributes to the progression of their pathology. Furthermore, changes in the nAChRs distribution and density in the NMJs are associated with diminished motor function. Here, we assess the structural integrity and stability of the synapses from transgenic mouse models of PD well before the onset of the disease by analyzing the NMJs of wide-spread musculature. This approach enabled us to elucidate regional and temporal patterns of loss to nAChR density and distribution. In addition, we correlate the progression of synaptic disassembly to motor behavior performance. Finally, we compare observed changes in the LRRK2 models to human skeletal muscle tissue. **MATERIAL AND METHODS**: We use LRRK2 (leucine-rich repeat kinase 2) transgenic mice (C57BL/6-Lrrk2tm4.1Arte, Taconic Biosciences) and C57BL/6J mice (The Jackson Laboratory). To evaluate motor behavior, we conducted motor coordination and function tests like grip strength, cylinder tests, and gait analysis. Mice were euthanized and muscles extracted and fixed in 4% PFA. Muscles were further dissected and labeled with Alexa594 αλπηα-bungarotoxin (α-BTX), mounted on slides, and imaged under the epifluorescent microscope to assess postsynaptic receptor density. To study nAChR dynamics, we labeled mice sternomastoid muscle in vivo and imaged their synapses over time. To analyze the presynaptic component of NMJs, we labeled the axon terminal and Schwann cells. Additionally, we analyzed human tissue from both PD and healthy subjects. **RESULTS:** LRRK2 transgenic mice exhibited a significant decline in motor performance and postsynaptic nAChR density compared to controls. nAChR dynamics and the overall structural integrity of the NMJ were altered. **CONCLUSIONS**: A pattern of changes in the NMJ exists well before the age of phenotypic presentation in mice. The observed early NMJ fragmentation and disassembly may represent a peripheral manifestation of disease that is relevant in the clinical setting.

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Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

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Program #/Poster #: PSTR016.02/C79

Topic: C.03. Parkinson's Disease

Support: NIH Grant 1R21NS123770-01

Title: The Cross-linking Activity of Transglutaminase 2 Mediates alpha-Synuclein Pathology in the Preformed Fibril Model of Synucleinopathy in Mice

Authors: *K. HASSANZADEH[1], M. A. TABARI[1], J. LIU[2], S. MADDILA[1], M. MOURADIAN[1];
[1]Rutgers Univ., Piscataway, NJ; [2]Neurol., Rutgers - Robert Wood Johnson Med. Sch., Piscataway, NJ

Abstract: The Cross-linking Activity of Transglutaminase 2 Mediates alpha-Synuclein Pathology in the Preformed Fibril Model of Synucleinopathy in Mice.K. Hassanzadeh, M A. Tabari, J. Liu, S. Maddila, M M. Mouradian **Abstract**The accumulation of aggregated α-Synuclein (α-Syn) is linked with neurodegeneration in synucleinopathies. Transglutaminase 2 (TG2), the most ubiquitous member of the transglutaminase family, is a multifunctional protein known for its protein crosslinking ability. Evidence has been developed for the presence of TG2-mediated crosslinking of α-Syn in postmortem brains affected with Parkinson's disease and Dementia with Lewy Bodies. Additionally, in vitro and cell based-experiments have shown that α-Syn is a substrate for TG2. Using α-Syn transgenic mice, we previously showed that elevated TG2 levels exacerbate α-Syn toxicity by promoting the formation of complex α-Syn structures, whereas TG2 deletion reduces α-Syn toxicity and improves behavioral performance. To further examine the role of TG2's crosslinking activity in α-Syn pathology, we created transgenic mice expressing a catalytically inactive mutant form of TG2 (TG2 Mu) devoid of its crosslinking activity only and compared them to TG2 transgenic mice overexpressing wild-type TG2 (TG2 Tg) and TG2 knockout mice (TG2 KO) in the α-Syn Preformed Fibril (PFF) model. Behavioral assessments 6 months post-PFF injections revealed that TG2 (Tg) mice exhibited the most pronounced decline in performance of all groups, while TG2 (KO) mice had the least deterioration. Notably, the decline in the behavioral performance of TG2 (Mu) mice was comparable to those observed in wild-type (WT) mice. Immunohistochemical studies of brain tissue sections showed that phosphorylated-α-Syn positive aggregates were more abundant in the striatum and substantia nigra of TG2 over-expressing mice injected with PFF compared with TG2 (KO) and TG2 (Mu) mice, while the levels of this marker in TG2 (Mu) mice were comparable to those in WT mice. Additionally, nigrostriatal dopaminergic neurons and terminals were more vulnerable to PFF in mice overexpressing wild-type TG2, but not in mice overexpressing the mutant form. These results indicate that the lack of the transamidase activity of the transgene in TG2 (Mu) mice results in a behavioral phenotype and pathological markers comparable to those of wild-type mice, thus, highlighting the crucial role of TG2 crosslinking activity in α-Syn aggregation, propagation and toxicity. Collectively, these findings support the potential for pharmacological tools that inhibit TG2-mediated cross-linking as a therapeutic strategy to modify the progression of α-synucleinopathies.

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Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

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Program #/Poster #: PSTR016.03/C80

Topic: C.03. Parkinson's Disease

Support: the National Natural Science Foundation of China

Title: Unique expression and function of PINK1-Parkin in the non-human primate brain

Authors: *Q. WANG[1,2], X. CHEN[1], S.-H. LI[3,2], X.-J. LI[1,2], W. YANG[4,2];
[1]Jinan Univ., Guangdong, China; [2]Guangdong key laboratory of non-human primate research, Guangzhou, China; [3]GHM Inst. of CNS Regeneration, Jinan Univ., Guangzhou, China; [4]Jinan Univ., Guangzhou City, China

Abstract: Mutations in PINK1 or Parkin can lead to early onset Parkinson's disease through a loss-of-function mechanism. However, current Parkin or PINK1 knockout rodent models do not exhibit neurodegeneration. Furthermore, there is a lack of strong in vivo evidence to support the theory that PINK1-Parkin deficiency affects mitophagy and induces neurodegeneration. In our recent work, we found that PINK1 and phosphorylated Parkin are selectively expressed in primate brains, though they were undetectable in rodent and even pig brains. CRISPR/Cas9-mediated deficiency of PINK1 affects neuronal survival by impacting protein phosphorylation, without altering mitochondrial protein expression and morphology. PINK1-targeting or aging reduces Parkin phosphorylation and increases the level of pS129-α-syn, thereby resulting in neuronal toxicity. Overexpression of wild-type Parkin, but not a mutant form that cannot be phosphorylated by PINK1, reduced the accumulation of pS129-α-syn in the monkey brains. Thus, using the non-human primate models, we identified PINK1-mediated Parkin phosphorylation as a key factor in PD pathogenesis and a promising target for therapeutic interventions.

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Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

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Program #/Poster #: PSTR016.04/C81

Topic: C.03. Parkinson's Disease

Support: Department of Defense PD170080P1 grant

Title: Investigating the impact of C. amycolatum colonization on Parkinson's Disease pathology and neuroinflammation in the Thy1-SNCA PD mouse model

Authors: *N. MUDIUM[1], A. S. HARMS[1], W. WON[1], J. WEBSTER[2], N. CORBIN-STEIN[2]; [1]Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; [2]Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Parkinson's Disease (PD) is a progressive movement disorder characterized by alpha-synuclein (a-syn) accumulation and the loss of dopaminergic neurons in the substantia nigra pars compacta, a region responsible for regulating movement. Recent research suggests that the early pathology of PD is influenced by gut barrier deterioration or gut dysbiosis. Distinct gut microbial profiles have been shown to increase circulating inflammatory molecules and a-syn aggregates thus leading to neurodegeneration. How gut dysbiosis drives pro-inflammatory mechanisms remains unknown. A potential pathway through which gut bacteria can act is by modulating neuroinflammation, a key driver of neurodegeneration in PD. A recent study identified Corynebacterium amycolatum, an opportunistic pathogen, to be disproportionately present in the gut of human PD patients. We hypothesized that C. amycolatum would enhance the PD behavioral phenotype, increase a-syn aggregation, and increase glial dysregulation in the Thy1-SNCA mouse model. 3-month-old Germ-Free Thy1-SNCA transgenic mice overexpressing human a-syn and non-transgenic controls either received or did not receive a C. amycolatum fecal transplant. Two cohorts were raised 1-month and 6-months post-transfer. The 6-month cohort underwent the Open Field test and Pole Test behavioral assays while brain tissue from both was labeled with pSer129, for misfolded a-syn, GFAP, for astrocytes, IBA1, for microglia, and MHCII, for neuroinflammation. Image J and StereoInvestigator were utilized to assess the area fraction, average cell body area, and branch number of microglia from blinded images. 1-month post-transfer, the transgenic C. amycolatum transplant group demonstrated a significant decrease in microgliosis in the ventral midbrain (vmb) and striatum and a significant decrease in MHCII in the vmb. Microglia cell body perimeter was increased in the vmb of the transplant group, as well. At 6 months, the transplant group demonstrated fewer motor deficits and a significant decrease in a-syn aggregates. No changes were observed in astrogliosis. Interestingly, our study provides evidence that the C. amycolatum condition attenuates microglial dysregulation, a-syn aggregation, and the PD phenotype, suggesting an early protective role of gut bacteria in the Thy1-SNCA mouse model.

Disclosures: **N. Mudium:** None. **A.S. Harms:** None. **W. Won:** None. **J. Webster:** None. **N. Corbin-Stein:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

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Program #/Poster #: PSTR016.05/C82

Topic: C.03. Parkinson's Disease

Support: NIH RF1 AG079199
NIH R01 DA049257

Title: Acute or progressive accumulation of neuromelanin in dopaminergic neurons of the SNc promote distinct stages of parkinsonian phenotype in mice

Authors: *A. DRUMOND-BOCK[1], K. CARTER[2], H. BLANKENSHIP[2,3], M. H. HIGGS[2], A. IANNITELLI[4], D. WEINSHENKER[4], M. J. BECKSTEAD[2];
[2]Aging & Metabolism Res. Program, [1]Oklahoma Med. Res. Fndn., Oklahoma City, OK; [3]Dept. of Phisiology, Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK; [4]Dept Human Genet., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Catecholaminergic neurons, including dopaminergic neurons of the substantia nigra pars compacta (SNc), naturally accumulate the pigment neuromelanin (NM) throughout life. While NM can be protective by neutralizing excessive dopamine (DA), metals, and protein aggregates into lipid rich organelles, excessive buildup during aging correlates with neurodegeneration associated with Parkinson's disease (PD). Despite its connection with PD, studies involving NM are challenging, because the brains of laboratory animals do not exhibit spontaneous aggregation of the pigment. However, production of NM in catecholaminergic neurons can be achieved via adenovirus-induced expression of human tyrosinase (hTyr), the rate-limiting enzyme for melanin synthesis in peripheral tissues. We have recently developed a dopaminergic-specific mouse model of accumulation of NM in the SNc, with the use of *DAT^{IREScre}* mice (expressing *Cre recombinase* under the dopamine transporter promoter). These mice received stereotaxic injections of adenovirus containing floxed *hTyr* gene (AAV-DIO-hTyr), which allows for expression of *hTyr* exclusively in DA cells. We generated acute and progressive phenotypes by injecting two dilutions of viral particles (full strength and 1:100). Our acute model exhibited expression of *hTyr* in approximately 90% of the DA neurons in the SNc, as early as 1 week post injection. By 3 weeks there was a drastic loss of tyrosine hydroxylase signal, associated with the formation of NM granules, which overtook most of the cytoplasm of these cells by week 5. Patch clamp electrophysiology showed disruption of pacemaker firing by 2 weeks, and behavioral studies confirmed locomotor impairment in these mice, which lost the ability to maintain rotarod balance, spent less time exhibiting ambulatory and exploratory behavior, and spent more time resting. In contrast, although our progressive model presented *hTyr* expression and NM accumulation in DA neurons of the SNc, optical density analysis revealed that the accumulation of NM in these animals after 8 weeks was only ~25% of the accumulation of NM observed in our acute model at 5 weeks. Animals in our progressive model displayed locomotor behavior very similar to control animals, and considerably better than our acute model. Overall, our results show that although DA-specific accumulation of NM can be successfully achieved, the degree at which these aggregates form defines how fast a parkinsonian phenotype is observed. The ability to induce acute or progressive accumulation of NM enables further understanding into the interaction between NM accumulation and the progression of PD.

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Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.06/C83

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS NS045962

Title: Striatal projection neuron hyperactivity in MPTP-treated macaques correlates with parkinsonism severity

Authors: *S. COLETTA[1], B. KOCHOIAN[2], C. SINON[2], T. YABUMOTO[3], S. M. PAPA[4]; [1]Emory Univ., ATLANTA, GA; [2]Neurosci., Emory Univ., Atlanta, GA; [3]Emory Natl. Primate Res. Ctr., Emory Univ., Atlanta, GA; [4]Neurol., Emory Univ., Atlanta, GA

Abstract: Parkinson's Disease (PD) is a progressive neurodegenerative disorder primarily characterized by the loss of nigrostriatal dopaminergic neurons and cardinal motor symptoms. The striatum, being the primary recipient of nigral projections, undergoes significant functional changes following dopamine (DA) depletion. In our previous studies involving advanced, severely parkinsonian non-human primates (NHPs), we observed significant increases in striatal projection neuron (SPN) activity. Moreover, a significant proportion of hyperactive neurons exhibited increased bursting activity which was suppressed, or markedly reduced, in response to L-Dopa administration. We also found similar changes in SPN activity patterns in patients with PD, but there are conflicting data on human recordings collected and analyzed with different methodologies.

To address these discrepancies and enhance the reliability of our analysis, we conducted a thorough retrospective analysis of our previously published datasets, implementing a standardized analysis framework and focusing specifically on units with high isolation scores (IS>0.7) to minimize confounding factors. Additionally, we explored correlations between SPN hyperactivity, bursting patterns, and local field potentials (LFPs) with behavioral features and the extent of DA cell loss. Our findings revealed a strong association between SPN hyperactivity and the severity of motor symptoms in PD, aligning with the notion that motor deficits appear only after a substantial loss of DAergic neurons. SPN hyperactivity is predominantly observed in models with significant motor disability (Motor Disability Score $\geq$ 15, using a standardized motor disability scale for MPTP-treated NHPs equivalent to Part III of the Unified Parkinson's Disease Rating Scale used for patients with PD). Moreover, striatal oscillatory activity is thought to reflect incoming cortical input, and exaggerated corticostriatal activity has been extensively documented in animal models of DA depletion, and indirectly in patients with PD in the form of excessive beta band oscillations. Thus, LFP analysis may help uncovering a link between SPN hyperactivity and aberrant corticostriatal inputs.

Overall, our data indicate that SPN dysfunctional state correlates with the progression of PD motor symptoms. These findings may contribute to understand the mechanisms underlying SPN hyperactivity and may provide insights into PD pathophysiology and new treatment strategies.

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Poster

PSTR016: Parkinson’s Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.07/C84

Topic: C.03. Parkinson’s Disease

Title: Tracking Parkinson's Disease Progression: Evaluating Animal Models for Drug Development

Authors: *K. PARK, J. LEE, S. LEE, Y. KIM, T. KIM, M. LEE, A. LEE, S.-Y. NA, P. J. SWEENEY, L. PARK;
Naason Sci., Cheongju-si, Korea, Republic of

Abstract: This study investigates Parkinson's disease (PD) progression using two animal models to clarify disease dynamics and refine therapeutic interventions. The models employed are alpha-synuclein pre-formed fibrils (αSyn PFF) injection and the Thy1-αSyn mouse model (Line 61) featuring human α-synuclein overexpression. Disease progression is evaluated through behavioral changes, fibril formation, neurofilament light chain (NF-L) as a marker of neuronal degradation, and dopamine levels across aging. The goal is to enhance the timing and efficacy of emerging drug treatments. Mice injected with αSyn PFF at two months of age were monitored for phosphorylated alpha-synuclein (pSer129) levels in the cortex and substantia nigra pars compacta (SNpc) from 1 to 8 months post-injection. An increase in pSer129 alpha-synuclein levels was observed starting from the first month. Behavioral tests, including wire hanging, pole, and grip strength, were conducted at 2, 6, and 8 months. While no differences were detected between wild-type (WT) and PD models at 2 months, significant differences in wire hanging ability appeared between 6 and 8 months, along with increased errors in the transverse beam test at 8 months. In the Thy1-αSyn mouse model, motor function tests such as the rotarod and transverse beam test (TBT) were performed between 4 and 12 months of age. Transgenic (TG) mice showed a more than two-fold decrease in rotarod performance starting at 4 months. TG mice also displayed a fivefold increase in step parameter error in TBT compared to WT, consistent with previous research findings. Cognitive performance differences were absent in the Y-maze test up to 12 months, but differences were noted in the Morris Water Maze (MWM) test at 9 months. Age-related increases in cerebrospinal fluid (CSF) NF-L levels were observed for the first time in this study, highlighting its potential as a novel PD biomarker. The study concludes that these animal models provide valuable insights into aSyn-induced Parkinson's disease progression, demonstrating age-related increases in biomarkers and behavioral deficits. These findings can inform the optimization of therapeutic interventions and aid in determining the most effective timing for new-drug efficacy trials.

Disclosures: K. Park: None. **J. Lee:** None. **S. Lee:** None. **Y. Kim:** None. **T. Kim:** None. **M. Lee:** None. **A. Lee:** None. **S. Na:** None. **P.J. Sweeney:** None. **L. Park:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.08/C85

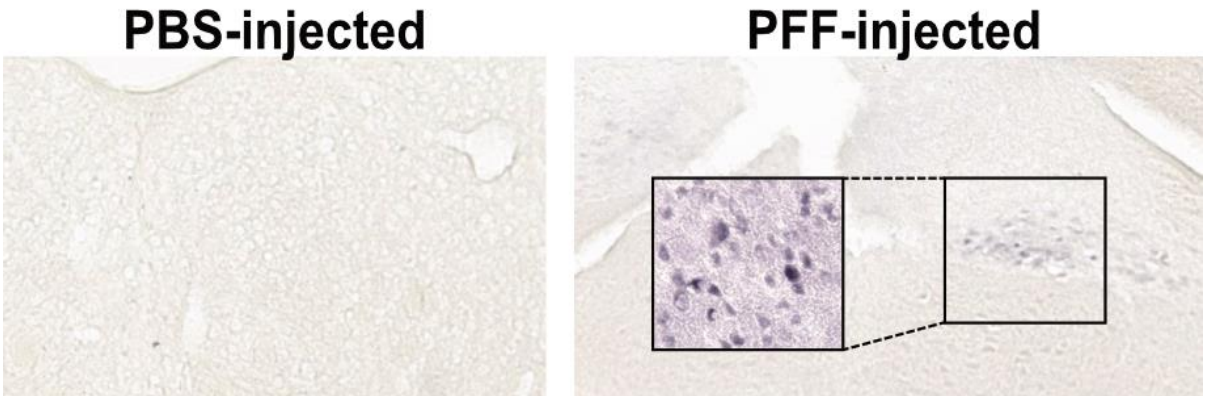
Topic: C.03. Parkinson's Disease

Support: NIDDK K08DK134872
NCATS UL1TR0001881, UCLA Clinical and Translational Science Institute (CTSI) KL2 Translational Science Award

Title: Persistence of central pathology in Parkin knockout mice following duodenal seeding of alpha-synuclein

Authors: A. H. YEHYA[1], H. LAM[2], Z. SHU[2], Y. JIN[3], C. PENG[3], N. T. MAIDMENT[2], *E. J. VIDELOCK[1];
[1]Dept. of Med., [2]Dept. of Psychiatry and Biobehavioral Sci., [3]Dept. of Neurol., UCLA, Los Angeles, CA

Abstract: Background & Hypothesis: Parkinson's Disease may begin in the gut. Rodent gut seeding models demonstrate that injection of alpha-synuclein (aSyn) preformed fibrils (PFFs) into the myenteric plexus results in seeding of endogenous aSyn and vagal propagation to the CNS. Aged rodents are more likely to develop persistent CNS pathology in this model of "gut-first" PD. Impaired mitophagy is implicated in PD pathogenesis and reduced in aging. Although mutations in the mitophagy regulator, Parkin, cause young onset PD, Parkin knockout (PKO) mice do not have a PD phenotype at baseline. We hypothesize that, similar to aged mice, PKO mice will be more susceptible to gut-first PD.
Methods: Male and female C57B6/J (WT) and PKO mice (age 3 months) were injected with a total of 6ug murine aSyn PFFs or PBS in the proximal duodenal muscularis (two sites, 3uL per injection). Mice (n=4 per group, 16 total) were sacrificed at 90- and 180-days post-injection (dpi). CNS aSyn pathology was measured by immunostaining for S129P aSyn. Staining per section (median 4 per region) was scored on a scale of 0 (none) to 5 (strong) in the medulla oblongata containing the dorsal motor nucleus of the vagus (DMV), midbrain containing the substantia nigra (SN), amygdala (AM), hippocampus (HI), cortex (CO) and olfactory bulb (OB).
Results: At 90 and 180 dpi, PFF-injected WT mice had increased aSyn pathology in the DMV (Fig 1, p=0.01) but this did not reach significance in PKO mice (p=0.15). At 90 dpi, weak (score 1) staining of cell bodies was seen in the SN in at least one section in 8/8 PFF-injected mice (WT and PKO) and in 2/8 PBS-injected mice. At 180 dpi, this staining pattern was present in 4/4 PFF-injected PKO mice and 2/4 PFF-injected WT mice. No SN aSyn pathology was observed in PBS-injected mice at this timepoint.
Conclusions: Similar to published studies, CNS aSyn pathology following gut-seeding of aSyn PFFs appears to reduce with time post injection. These preliminary findings suggest that pathology may persist in PKO mice, which would support our hypothesis; however, a larger sample and additional timepoints (ongoing) are required.



Disclosures: **A.H. Yehya:** None. **H. Lam:** None. **Z. Shu:** None. **Y. Jin:** None. **C. Peng:** None. **N.T. Maidment:** None. **E.J. Videlock:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.09/C86

Topic: C.03. Parkinson's Disease

Support: NIH Grant R37NS071251

Title: LRRK2 R1441C but not G2019S mutation compromises dopaminergic neuronal survival

Authors: ***A. SHAHAPAL**[1], L. CUI[2], J. KANG[1], J. SHEN[3];
[1]Brigham and Women's Hosp., Boston, MA; [2]Dept. of Neurol., Brigham and Women's Hospital/Harvard Med. Sch., Boston, MA; [3]Neurol., Brigham and Women's Hosp., Harvard Med. Sch., Boston, MA

Abstract: Mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common genetic cause of Parkinson's disease (PD), but the pathogenic mechanism remains unresolved. Our development of *Lrrk* double knockout (DKO) and dopaminergic (DA) neuron- specific conditional DKO mice revealed an essential, cell intrinsic role of LRRK in the survival of DA neurons in the aging brain. G2019S in the kinase domain of LRRK2 is the most common mutation but exhibits lower penetrance and higher age of onset, whereas R1441C in the GTPase domain is highly penetrant and is one of the three mutations (C/G/H) identified in the R1441 residue, highlighting its significance for PD pathogenesis. In this study, we compare the consequences of the *Lrrk2* G2019S vs. R1441C knockin (KI) alleles in DA neuron survival through the generation of G2019S and R1441C KI mice in the presence or the absence of LRRK1, the functional homologue of LRRK2. We found that in the absence of LRRK1, R1441C but not G2019S KI alleles result in age-dependent, progressive reductions of DA neurons in the substantia nigra pars compacta (SNpc) at the ages of 20 and 25 months of age, proceded by

elevated apoptotic DA neurons at 15 months. Furthermore, LRRK2 kinase activity is similarly increased in the cortex and the dissected ventral midbrain of R1441C and G2019S KI mice in the presence or the absence of LRRK1, as shown by the similarly elevated levels of phosphorylated Rab12, Rab8A, Rab10, physiological substrates of LRRK2. Taken together, these findings show that LRRK2 R1441C but not G2019S compromises its physiological function in support of DA neuron survival during aging, and that the increase of LRRK2 kinase activity by R1441C and G2019S mutations is dissociated from their impact on DA neurodegeneration.

Disclosures: A. Shahapal: None. **L. Cui:** None. **J. Kang:** None. **J. Shen:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.10/C87

Topic: C.03. Parkinson's Disease

Support: DoD NETP 13204752
NIDDK R01 DK12409
NINDS R01 NS104565
Anne M. and Phillip H. Glatfelter III Foundation

Title: Deeplabcut (DLC) to automate behavioral analysis of parkinsonism.

Authors: *N. J. RANGOONWALA[1,2], K. M. LE[3], V. V. PESHATTIWAR[3], C. C. SWAIN[3], D. POKHAREL[3], T. WHITE[3], K. VENKITESWARAN[3], T. SUBRAMANIAN[3];
[1]Univ. of Toledo Med. Ctr., Toledo, OH; [2]Neurology, University of Toledo, Toledo, OH; [3]Neurol., Univ. of Toledo, Toledo, OH

Abstract: Behavioral assessment of parkinsonism often relies on human rater evaluation. However, human biases and variability necessitate larger sample sizes to maintain validity, leading to extensive video analysis, and limiting researchers' time. Recent Artificial Intelligence (AI) and Machine Learning (ML) advancements enable efficient data analysis, offering unbiased decision-making and consistency across scenarios, bridging inter-rater differences. While not fully automating jobs, AI/ML boosts productivity when properly trained with diverse data. This study aims to show that AI/ML can assist in the analysis of rat parkinsonian behavioral studies to reduce labor dependence while still maintaining accuracy. DeepLabCut (DLC), an animal pose estimation software, was used to analyze motor behavior in video recordings of parkinsonian Sprague Dawley rats while they performed the stepping test (n = 24). The stepping test involves observing the animal's locomotor function and motor coordination while it is guided across a flat surface (Anselmi 2018). The amount of adjusting steps was counted over the 1-meter distance. 28 videos (n=24 + 4 training videos) were fed into DLC, which then selected 20 frames per video using a k-nearest neighbors' algorithm and subsequently labeled to train the model. This one-time training process took 3 hours. The output, which has the tracked coordinates of the

forepaw being tested, was fed into a script in R to plot Δy between consecutive frames. The positive peaks were counted as one step and large negative peaks were counted as a reset or side switch. The counts for each video were then compared to an independent manual rater. This preliminary study resulted in a 98.37% accuracy rate by the DLC-assisted count when compared to a human rater. The intraclass correlation coefficient was computed to assess the agreement between the manual scoring method and the DLC-assisted method described above in the 28 videos. There was good absolute agreement between the two scoring methods, using the two-way random effect model, kappa = 0.9, $p<0.0001$. It takes 10-15 minutes to go through each video manually, but the DLC-assisted scoring resulted in 3-4 minutes per video. These results show that DLC-assisted scoring produced results that could be on par with manual scoring. Additionally, this shows a feasible avenue to integrate AI/ML in parkinsonian behavioral studies to reduce the workload for analysis and eventually, fully automating such tasks.

Disclosures: N.J. Rangoonwala: A. Employment/Salary (full or part-time):; Full time. **K.M. Le:** A. Employment/Salary (full or part-time):; Full time. **V.V. Peshattiwar:** A. Employment/Salary (full or part-time):; Full time. **C.C. Swain:** A. Employment/Salary (full or part-time):; Full time. **D. Pokharel:** A. Employment/Salary (full or part-time):; Full time. **T. White:** A. Employment/Salary (full or part-time):; Full time. **K. Venkiteswaran:** A. Employment/Salary (full or part-time):; Full time. **T. Subramanian:** A. Employment/Salary (full or part-time):; Full time. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Supernus, Neurocrine, Acadia. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CRC Press and Founder of StereoRx..

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.11/C88

Topic: C.03. Parkinson's Disease

Support: SFN Grant P500PB_214355

Title: Anxa1+ dopamine neurons: vulnerability and function in mouse models of Parkinson's disease progression

Authors: *A. CONTESTABILE[1,3], I. MANTAS[4,3], V. SKARA[4,3], I. S. SANTOS[4], R. FILOGRANA[2], K. MELETIS[4,3];
[1]Dept. of Neurosci., [2]Dept. of Med. Biochem. and Biophysics, Karolinska Institutet, Stockholm, Sweden; [3]Aligning Sci. Across Parkinson's (ASAP) Collaborative Res. Network, Chevy Chase, MD; [4]Karolinska Inst., Stockholm, Sweden

Abstract: Parkinson's disease (PD) stands as the second most prevalent neurodegenerative disorder globally, marked by incapacitating motor symptoms including bradykinesia, rigidity,

tremor, and postural instability. A prevailing hypothesis within PD research implicates the progressive demise of susceptible dopamine (DA) neurons, with a subset degenerating early in the disease course. This study endeavors to elucidate the molecular and behavioral modifications occurring during the prodromal phase of PD, preceding the manifestation of cardinal symptoms. Leveraging MitoPark and 6-OHDA models at early degeneration stages, we identified loss in Anxa1-expressing DA neuron subpopulation. At the functional level, optogenetic experiments showed no link between Anxa1+ DA release and self-stimulation, but machine learning analysis of open field exploration revealed specific differences akin to early PD phenotypes in MitoPark and 6-OHDA models. Furthermore, reaching test experiments highlighted impaired strategy adaptation and motor learning in mice with silenced Anxa1+ neurons. In summary, we propose that Anxa1+ DA neurons play a key role in early motor and non-motor deficits in the prodromal stage of PD.

Disclosures: A. Contestabile: None. **I. Mantas:** None. **V. Skara:** None. **I.S. Santos:** None. **R. Filograna:** None. **K. Meletis:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.12/C89

Topic: C.03. Parkinson's Disease

Support: MJFF-022863
PF-SF-JFA-1040267

Title: Detailing the Time Course of Parkinson's Disease Cholinopathy: Insights from a Novel Mouse Model

Authors: *K. UDOBI[1], V. ALEMAN[2], C. KONJA[4,2], M. EZEIZA-ORTEGA[5], S. GROSSEN[4], R. C. EVANS[3];
[2]Neurosci., [1]Georgetown Univ. Med. Ctr., Washington, DC; [3]Neurosci., Georgetown Univ. Med. Ctr., Washington DC, DC; [4]Neurosci., Georgetown Univ., Washington, DC; [5]Children's Natl. Med. Ctr., Washington, DC.

Abstract: Parkinson's Disease (PD) cholinopathy, characterized by the degeneration of cholinergic neurons within the pedunculopontine nucleus (PPN), presents challenges in understanding PD symptom progression. The PPN, crucial for gait, posture, and balance control, undergoes significant, but variable, degeneration in PD, particularly affecting its cholinergic neurons. As certain PD symptoms that resist dopamine-based therapies may respond to deep brain stimulation targeting the PPN, we are developing a novel mouse model to isolate the role of cholinergic PPN degeneration in symptom development and assess the time course of these symptoms. To evaluate the time course of symptom development in PD cholinopathy, we developed a novel mouse model using ChAT-Cre-Ai9tdTomato mice and a cre-dependent

caspase. Previous toxin-based methods lesioning the PPN in rats provided insights into PD cholinopathy but are limited by dose-dependent selectivity and potential off-target effects of the toxin used. To address these limitations, we employed a cre-dependent caspase to selectively lesion cholinergic PPN neurons in ChAT-cre mice of both sexes. This non-toxin-based method offers high specificity crucial for elucidating the contribution of cholinergic PPN degeneration to PD symptomatology. We find reduced cholinergic PPN neurons following caspase induction accompanied by mild motor and non-motor behavior alterations. Specifically, lesioned mice demonstrate slightly slower movement on a balance beam but increased locomotion in an open field, alongside reduced startle responses and an increased time in the open areas of an elevated zero maze. This study illuminates the intricate interplay between cholinergic PPN degeneration and PD symptomatology, providing a valuable framework for understanding disease progression. Moreover, our findings underscore the potential of the proposed mouse model in capturing the dynamics of PD cholinopathy.

Disclosures: K. Udobi: None. **V. Aleman:** None. **C. Konja:** None. **R.C. Evans:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.13/C90

Topic: C.03. Parkinson's Disease

Title: Deficiency of Rab39b-induced autophagy impairment upregulates α-synuclein and causes degeneration of dopaminergic neurons in mouse model of Parkinson's disease.

Authors: *C.-C. CHIU;
Chang Gung Univ., TAOYUAN, Taiwan

Abstract: RAB39B deficiency resulting from deletion or mutation of RAB39B gene causes X-linked Parkinson's disease (PD) in male patients. Male Rab39b knockout ($Rab39b^{-/Y}$) mice were prepared to investigate pathogenic mechanisms underlying RAB39B paucity-induced degeneration of substantia nigra (SN) dopaminergic neurons. $Rab39b^{-/Y}$ mice displayed PD motor deficits and neurodegeneration of SN dopaminergic cells. Autophagy impairment and upregulated neurotoxic α-synuclein were observed in SN of $Rab39b^{-/Y}$ mice. Autophagy activator rapamycin reversed α-synuclein upregulation and ameliorated PD phenotypes in $Rab39b^{-/Y}$ mice. Rab39b deficiency-induced increase of α-synuclein within endoplasmic reticulum (ER) and mitochondria activated ER stress-triggered apoptotic cascade and caused mitochondrial dysfunction and oxidative stress, respectively. Rab39b deficiency -induced α-synuclein overexpression caused SN microglial activation, leading to NLRP3 inflammasome activation, upregulation of IL-1β, IL-18 or TNF-α and activation of apoptotic neuronal death cascades. Our data suggest that RAB39B deficiency causes neurodegeneration of SN dopaminergic cells and PD by impairing autophagy and upregulating pathologic α-synuclein.

Disclosures: C. Chiu: None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.14/C91

Topic: C.03. Parkinson's Disease

Support: R01

Title: Striatal injection of preformed fibrils induces changes in erasmus ladder performance and motor cortex neuronal excitability

Authors: *J. REINHARDT, N. E. CHAMBERS, D. HALL, D. NABERT, M. MILLETT, M. S. MOEHLE;
Pharmacol. and Therapeut., Univ. of Florida, Gainesville, FL

Abstract: One hallmark of Parkinson's disease is the pathological development of α-synuclein aggregates. The function of these aggregates on motor behavior and other behaviors are unknown. Therefore, in the current study we injected preformed fibrils (PFFs) or control monomeric α-synuclein (monomer) bilaterally into the striatum of mice. We then tested motor behavior in the Erasmus Ladder at various time points after PFF injection. We also performed ex vivo electrophysiology recordings in the motor cortex in neurons which expressed α-synuclein aggregates and those which did not. Overall, we observed that PFF mice showed some deficits in the Erasmus ladder performance which changed according to the timeline of PFF injection. Our findings suggest that striatal injection of PFFs and subsequent spread of these fibrils induces behavioral differences from monomer controls. Additionally, our ex vivo electrophysiology recordings revealed hypoexcitability in neurons in the motor cortex which express α-synuclein aggregates. Taken together, our findings indicate that PFFs injected into the striatum spread to other brain areas, thus inducing behavioral and electrophysiological changes. Future research should further investigate these changes to better understand at what point these changes occur and to find potential therapeutic targets to alleviate these behavioral deficits.

Disclosures: J. Reinhardt: None. **N.E. Chambers:** None. **D. Hall:** None. **D. Nabert:** None. **M. Millett:** None. **M.S. Moehle:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.15/

Topic: C.03. Parkinson’s Disease

Title: Study of motor symptoms and non-motor symptoms in a double-hit model of Parkinson's disease

Authors: *W. MAYO ARELLANO[1,2], I. PARRA[3], E. BAUTISTA RODRIGUEZ[4], J. L. GONGORA-ALFARO[5], V. PALAFOX-SANCHEZ[6], L. MARTINEZ MENDIETA[3]; [1]BUAP, Puebla, Mexico; [2]BENEMERITA UNIVERSIDAD AUTONOMA DE PUEBLA, Puebla, Mexico; [3]Benemérita Univ. Autónoma De Puebla, Puebla, Mexico; [4]Fac. of Hlth. Sci., UPAEP, Tlaxcala, Mexico; [5]Neurosci., Univ. Autonoma de Yucatan, Merida, Mexico; [6]Inst. Tecnológico y de Estudios Superiores de Monterrey, Monterrey, Mexico

Abstract: Study of motor symptoms and non-motor symptoms in a double-hit model of Parkinson's disease *[1] **W.A Mayo-Arellano**, [1]I. Parra [1]Isabel Martínez-García, [2]V. Alatriste, [1]L. Mendieta, [3]V. Palafox-Sánchez, [4]E. Bautista Rodriguez [1]Laboratorio de Neuroquímica-BUAP, [2]Laboratorio de Neuroendocrinología BUAP [3]Instituto Tecnológico y de Estudios Superiores de Monterrey [4]Universidad de Tlaxcala **Disclosures W.A Mayo-Arellano**: None, **I. Parra:** None **L. Mendieta**: None, **V. Palafox-Sánchez**: None, **I. Martínez-García**: None, V. Alatriste: None, **Abstract**Parkinson's disease (PD) ranks second after Alzheimer's disease among the most common neurodegenerative disorders. A global incidence rate of 17 per 100,000 people per year has been reported. The main clinical feature of PD is motor impairment, characterized by resting tremor, muscle rigidity, and postural instability. However, non-motor symptoms (NMS), including pain, sensory disturbances (hyposmia), and gastrointestinal (GI) dysfunction, have long been recognized. These symptoms, in particular have been considered valuable for the early diagnosis of PD because they can occur years before the onset of motor symptoms. In this study, a PD model was generated to evaluate GI dysfunction associated with intestinal dysbiosis caused by antibiotics and neuroinflamation caused by lipopolysaccharide (LPS) in striatum in rats. We used this double-hit model to study the dopaminergic damage, microglial activation, motor behaviors, and intestinal activity parameters and muc-2 expression in the distal colon. Male Wistar rats (n=7 per group) were used, to which two antibiotics doses were administered o.p, amoxicillin (40mg/kg) and vancomycin (32mg/kg), along with an intra-striatal injection of LPS (32µg/2µL). Subsequent evaluations were conducted 7 and 8 days after LPS administration. The results obtained show that the "double-hit" animals exhibit a decrease of TH immunoreactivity in the striatum and the number of TH-positive neurons in SNpc. Regarding motor symptoms, "double-hit" animals show a decrease 10% in the use of both limbs in the cylinder model compared to the control group. However, when motor coordination was evaluated using the test-rotarod, no significant differences were found. Regarding non-motor symptoms, the "double-hit" decreased the pellet output in 1 hour, in compare to the control, and the cecum weight is also increased. In conclusion the "double-hit" model results useful to study motor and non-motor symptoms in EP.

Disclosures: W. Mayo arellano: None. **I. Parra:** None. **E. Bautista Rodriguez:** None. **J.L. Gongora-Alfaro:** None. **V. Palafox-Sanchez:** None. **L. Martinez Mendieta:** None.

Poster

PSTR016: Parkinson’s Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.16/C92

Topic: C.03. Parkinson's Disease

Support: NINDSRO1NS102257
T32NS095775
NIHNINDSF31NS129277-01

Title: Gbal444p mutant expression and microglial activation in limbic brain regions relevant to parkinson's disease

Authors: *E. BERRY[1], L. A. VOLPICELLI-DALEY[2];
[1]Univ. of Alabama at Birmingham, Bessemer, AL; [2]UAB, Birmingham, AL

Abstract: *GBA1* heterozygous mutations are a prevalent genetic risk factor for Parkinson's disease (PD) development. *GBA1*, which encodes for the lysosomal enzyme, glucocerebrosidase (GCase), is expressed ubiquitously across various cell types. Heterozygosity of the GBA1 L444P mutation ($GBA1^{+/L444P}$) is associated with a 5.6-fold increased risk of cognitive impairments. Furthermore, microglia activation is enhanced in *GBA1* mutation carriers. However, the contribution of GBA1L444P heterozygous expression on microglia activation is not fully understood. In this study, we used male and female 12-month-old $GBA1^{+/L444P}$ expressing mice and their wildtype littermates ($GBA1^{+/+}$) as controls. To assess microglia activity, immunofluorescence and confocal microscopy was performed for CD68 and Iba1 in the dentate gyrus and entorhinal cortex of the hippocampus. IMARIS software and the machine learning algorithm was used to reconstruct microglial branching. Understanding microglia activation in the hippocampus will help elucidate the underlying cellular mechanisms of cognitive impairments due to GBA1L444P expression.

Disclosures: E. Berry: None. **L.A. Volpicelli-Daley:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.17/C93

Topic: C.03. Parkinson's Disease

Title: Characterization of the Line61 Mouse Model of Parkinson's Disease

Authors: C. L. TORTURO, A. GHAVAMI, *S. RAMBOZ;
PsychoGenics, Paramus, NJ

Abstract: Alpha-synuclein is a presynaptic neuronal protein that is linked to Parkinson's Disease (PD) and contributes to disease pathogenesis. The Thy-1 Line61 mouse model of Parkinson's disease expresses human α-synuclein under the Thy-1 promoter resulting in neuronal overexpression. We sought to build on previous research by characterizing the model and identifying robust readouts that can be used to determine the efficacy of disease modifying therapies for Parkinson's disease. Heterozygous Line61 mice were tested in a battery of behavioral assessments. Line61 mice exhibited motor deficits as early as 9 weeks of age and gait deficits as early as 13 weeks of age. Functional readouts displayed deficits in neuromuscular function at 6 months of age, reduced mEPSC frequencies, and decreases in evoked striatal dopamine release. From a pathological perspective, increased total and pSer129 α-synuclein levels were observed in midbrain tissues, increased total human α-synuclein and aggregates were observed in cortex, striatum, and hippocampus, as well as increased hyperphosphorylated α-synuclein levels overall. Concluding remarks are pending additional data analysis. Our goal is to further characterize this model for testing disease modifying therapies for Parkinson's Disease.

Disclosures: C.L. Torturo: None. **A. Ghavami:** None. **S. Ramboz:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.18/C94

Topic: C.03. Parkinson's Disease

Support: PAPIIT IN205321
PAPIIT IN218124
Technical assistance Espino-Saldaña E, Alan Gonzalez, Andrea Quijada

Title: Longitudinal Behavioral Study of a Moderate hemi Parkinson disease model in Mice

Authors: *I. GONZALEZ HERNANDEZ, D. GASCA, V. CALDERON, A. MARTINEZ, A. HERNANDEZ;
Neurobiologia Mol. y Celular, Inst. de Neurobiologia UNAM, campus Juriquilla, Santiago de Querétaro, Mexico

Abstract: Parkinson's disease (PD) is a neurodegenerative disease characterized by a loss of nigrostriatal dopaminergic innervation into the striatum. Different murine models to study the physio-pathological changes as a consequence of the dopamine loss have been developed. Selective elimination of dopaminergic neurons has been performed by a 6 hydroxidopamine (6 OHDA) neurotoxin; however, this model shows an acute and fast neuronal death different than PD, here we propose a variation on this model by intra-striatal injection of the 6 OHDA with partial elimination of dopaminergic innervation and longitudinal analysis of the neurodegeneration by different behavioral test.Two months old C57 male mice were anesthetized using ketamine/xylazine. 6 OHDA was prepared in saline solution (0.1 % ascorbic acid) in 8

mg/ml. Three sites of injection into the striatum were selected (1 ul by site), sham group only receive the vehicle injection. All surgeries were performed in sterilized condition and in agreement with the guidelines of the UNAM ethical committee. After surgeries the subjects were maintained in 12 hr dark/light cycle, water, and food ad libitum until the behavioral evaluation. Behavioral tests at 4 and 8 weeks after injury were performed. Here, we evaluate the spontaneous turn behavior during 10 minutes without use any dopaminergic drug stimulation, the locomotor activity, and the stereotypical behavior in the open field test and the rotarod performance. Results obtained indicates a reduction on the locomotor activity measured on the open field 4 weeks after lesion and maintain at least for 8 weeks, in contrast ipsilateral turns were observed as maximum 4 weeks after lesion and a reduction to 50% after 8 weeks without any change on the motor skill learning performed in the acceleration rotarod. In conclusion, partial elimination of dopaminergic innervation into the striatum produces a progressive and partial recovery of the motor imbalance observed at least 8 weeks after the unilateral lesion.

Disclosures: I. Gonzalez Hernandez: None. **D. Gasca:** None. **V. Calderon:** None. **A. Martinez:** None. **A. Hernandez:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.19/C95

Topic: C.03. Parkinson's Disease

Title: Exploring mechanisms of Rab39b-linked Parkinson's disease in rodent models

Authors: *A. L. BERGSMA[1], A. V. OFFERMAN[2], K. A. SIPPLE[2], D. J. MOORE[2]; [1]Moore Lab., Van Andel Inst., Grand Rapids, MI; [2]Dept. of Neurodegenerative Sci., Van Andel Inst., Grand Rapids, MI

Abstract: Parkinson's disease (PD) is a common neurodegenerative movement disorder. Although the majority of PD cases are idiopathic, 5-10% of cases are inherited and caused by mutations in individual genes. Rab proteins are a family of small GTPases known to function as master regulators of vesicular trafficking that have also recently been implicated in the pathogenesis of PD. Loss-of-function mutations in the *RAB39B* gene are known to cause an X-linked dominant, early-onset form of PD and intellectual disability. How RAB39B dysfunction contributes to the neurodegeneration found in PD remains unclear. RAB39B is a neuronal-specific protein that is localized to the *trans*-Golgi network and plays a role in recycling vesicles between the Golgi and pre-synaptic compartment or endosomes. PD-linked mutations in RAB39B have been shown to alter its subcellular localization or protein stability, subsequently inducing impaired membrane association and function. In addition, RNAi-mediated gene silencing of *RAB39B* leads to reduced levels of α-synuclein protein in cultured neurons, suggesting a role in regulating α-synuclein homeostasis. Here, we explore the role of RAB39B in driving neurodegeneration in PD using a series of rodent models. Using *RAB39B* knockout (KO)

mice as a novel model of PD, we demonstrate that KO mice exhibit behavioral disinhibition, memory and motor deficits by 12 months of age. We are currently investigating the underlying neuropathology associated with these phenotypes. We are also exploring the relationship between RAB39B and α-synuclein-induced pathology and neurodegeneration by delivering α-synuclein PFFs to the striatum of KO mice, or by crossing KO mice to human A53T-α-synuclein transgenic mice. We have developed additional tools such as AAV2/6-RAB39B vectors to evaluate the neuroprotective effects of wild-type RAB39B in the rodent brain, and confirm whether PD-linked mutations (G192R) act via a loss-of-function mechanism. Finally, we are employing tools such as APEX2-based proximity labeling and cell painting assays to elucidate the normal function of RAB39B and the pathogenic mechanisms of PD-linked mutations, which will provide important insight into the pathophysiology of PD.

Disclosures: A.L. Bergsma: None. **A.V. Offerman:** None. **K.A. Sipple:** None. **D.J. Moore:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.20/C96

Topic: C.03. Parkinson's Disease

Title: Evaluating the Long-Term Behavioral Restoration and Dopamine Release Capacity from Mesenchymal-Derived Neuronal Stem Cell Transplantation Due to Encouraged Functional Integration with Varying Levels of Complex Limb-Use Use and Optogenetic Stimulation in a 6-OHDA Rat Model of Parkinson's Disease

Authors: *T. L. CAMMARANO[1], M. H. PAYTAS[2], N. T. BOND[2], C. M. GRANUM[2], S. M. GALIK[3], H. D. GEROW[2], K. ANDERSON[3], M. I. SANDSTROM[4];
[1]Neurosci. Grad. Program, [2]Neurosci., [3]Exptl. Psychology Grad. Program, Central Michigan Univ., Mount Pleasant, MI; [4]Psychology & Neurosci., Central Michigan Univ. Grad. Program In Neurosci., Mount Pleasant, MI

Abstract: While we've known the progressive idiopathic neurodegeneration exhibited in Parkinson's disease (PD) predominantly affects motor function as nigrostriatal dopaminergic (DA) neurons are lost, its treatment has yet to progress far since the advent of Levodopa. Its hallmark symptoms of tremor, rigidity, and bradykinesia are ameliorated in an increasingly challenged manner by either this pharmacology or, alternatively, deep brain stimulation. Yet these treatments disappoint due to diminished integrated host control. Increasing this control would likely correspondingly increase therapeutic effect. While replacing lost DA neurons seems ideal, this depends on such neurons being managed by the host. Our laboratory has been investigating utilizing bone marrow mesenchymal stem cells after differentiating them to exhibit DA neuron properties and inserting a transgenic construct engineered to respond to DREADD generated light (coelenterazine; CTZ) optogenetically. Thus, direct stimulations are engaged in

concert with active swimming in a manner we've found helps these transplants integrate with host control, and better support behavioral recovery. Initially such studies yielded promising short-term results, prompting our further exploration into long-term viability and functional support derived from this strategy. A pilot study revealed a trend of variable levels of cell integration, appearing to improve according to exercise regimen, suggesting a potential interaction between swimming opportunities and transplantation efficacy. This represents an exciting finding that may enhance disease treatments. Building on these findings, the presented work will extend explorations to include microdialysis measurements of activity-correlated transplant-derived DA release from freely moving subjects. This methodology aimed to verify that early stimulated cells not only integrate into the host brain, but also manage controlled DA release to facilitate appropriate behavioral responses. Contrary to common conceptions of the versatility or utility of these adult-derived mesenchymal-sourced stem cells, this strategy appears to provide sustainable, translational, long-term stabilization of motor function without the complications associated with traditional pharmacological treatments.

Disclosures: T.L. Cammarano: None. **M.H. Paytas:** None. **N.T. Bond:** None. **C.M. Granum:** None. **S.M. Galik:** None. **H.D. Gerow:** None. **K. Anderson:** None. **M.I. Sandstrom:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.21/C97

Topic: C.03. Parkinson's Disease

Support: ASAP-000592

Title: Senescence and neuroinflammation in D620N VPS35 mouse models of Parkinson's disease

Authors: *M. ERB[1], Y. MA[2], X. CHEN[1], A. OFFERMAN[3], D. J. MOORE[4];
[1]Van Andel Res. Inst., Grand Rapids, MI; [2]VAI, Grand Rapids, MI; [3]Van Andel Inst., Grand Rapids, MI; [4]Dept. of Neurodegenerative Sci., Van Andel Inst., Grand Rapids, MI

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative movement disorder, with advanced age being a major risk factor. One hallmark of aging that may contribute to the development of neuropathology in PD is the accumulation of senescent cells. Cellular senescence is characterized by irreversible cell cycle arrest, resistance to apoptosis, morphological changes and activation of a senescence-associated secretory phenotype (SASP), where cells secrete pro-inflammatory factors. Cells can become senescent in response to a variety of age-related factors including oxidative stress, mitochondrial dysfunction, epigenetic alterations or genomic instability. Although the chronic inflammation caused by SASP is detrimental to tissue health in a variety of tissues, little is known about senescence in brain cells.

Our work seeks to assess the relationship between senescence and PD neuropathology in a model of late-onset familial PD. A D620N mutation in *VPS35* causes late-onset, autosomal dominant PD. D620N VPS35 knockin mice develop progressive yet modest dopaminergic neurodegeneration in the substantia nigra and accumulate pretangle-like tau abnormalities over 15 months. Additionally, the AAV-mediated overexpression of human D620N VPS35 in the nigra causes dopaminergic neurodegeneration over 12 weeks. Here, we evaluate these two mouse models of *VPS35*-linked PD for cellular senescence. We find no change in classic markers of cellular senescence, including p16 or p21 expression, or nuclear Lamin-B1 levels. In some disease models, the removal of senescent cells reduces local chronic inflammation and promotes tissue repair. To assess the effects of systemic senescent cell removal, AAV2/6-D620N VPS35 mice were treated with Dasatinib and Quercetin (D/Q), a senolytic cocktail known to promote apoptosis of senescent cells. In this model, D/Q treatment has no effect on nigrostriatal pathway dopaminergic neurodegeneration or the accumulation of abnormal tau. Conversely, adult D620N VPS35 knockin mice received lipopolysaccharide (LPS) administration to induce acute systemic inflammation. After 7 days, we observe mild neuroinflammation in the cortex and striatum of all LPS-injected mice, but without differences between wild-type and D620N VPS35 knockin mice. LPS-injection did not unmask dopaminergic neurodegeneration in the nigra of these mice. To further assess cellular senescence in D620N VPS35 knockin mice, we are currently evaluating single-nucleus RNAseq from ventral midbrain tissue for senescence-related gene expression profiles. Our studies will provide important insight into the contribution of cellular senescence to late-onset PD.

Disclosures: M. Erb: None. **Y. ma:** None. **X. Chen:** None. **A. Offerman:** None. **D.J. Moore:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.22/C98

Topic: C.03. Parkinson's Disease

Support: Cohn Research Fellowship
CHS Pilot Grant Program

Title: Repeated amphetamine treatments in an adolescent rat model of ADHD is associated with striatal mitochondrial dysfunction and parkinsonian-like motor symptoms in adulthood

Authors: *A. L. PERSONS[1], R. ROMAY-TALLON[2], A. BROWN[2], C. GONZALEZ[2], T. NAPIER[3];
[1]RUSH Univ., Chicago, IL; [2]Neurolog. Sci., [3]Dept. of Psychiatry and Behavioral Sci., RUSH Univ. Med. Ctr., Chicago, IL

Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder that usually is diagnosed in early childhood. According to the 2022 National Survey on Child Health, it was estimated that 6.4 million children (10.5%) between the ages of 3 and 17 had a diagnosis of ADHD, and approximately 62% of these received ADHD medication. Common medications used to treat ADHD include stimulants such as methylphenidate and amphetamines; however, the long-term consequences of stimulant treatment during adolescence are largely unknown. An epidemiological study revealed that individuals with ADHD have a two-fold risk for developing a basal ganglia or cerebellar disorder (including Parkinson's disease; PD) later in life; this risk increases to six-fold if ADHD was treated with stimulants (Curtin *et al. Neuropsychopharmacology*, 2018). The identification of risk factors for developing PD is of great interest and the current study reveals a potentially unexplored "pathway to PD". Mitochondrial health is important for normal cell function and energy production, and mitochondrial dysfunction is implicated in ADHD and the pathogenesis of PD. We used a validated model of ADHD, spontaneously hypertensive Wistar-Kyoto (SH) rats, to test the hypothesis that SH rats treated with amphetamine during adolescence will develop behavior and brain pathology that mirror early stages of PD as adults. Young male SH rats (aged 4 weeks; n=16) and age-matched Wistar-Kyoto controls (WKY; n=16) were treated with escalating doses of *d*-amphetamine (A; 0.5 – 2mg/kg, sc) or vehicle (V; 1mL/kg, sc) for four weeks. As behavioral indices of PD, two common rat motor homologs of early-stage motor symptoms, postural instability and akinesia, were quantified once per week for five weeks after treatment ended. PD-like motor symptoms emerged in SH/A rats by three weeks post-treatment. By week five, SH/V and WKY/A rats demonstrated significant postural instability (compared to WKY/V rats), and this effect was exacerbated in SH/A rats (two-way ANOVA; $p<0.05$). Only SH/A rats developed akinesia by week five (two-way ANOVA; $p<0.05$). To determine if these behaviors were driven by PD-like brain pathology, we evaluated the density of tyrosine hydroxylase (TH) and mitochondrial damage (*via* cytochrome c translocation) in the striatum. While there was no loss of TH in the striatum, there was a significant increase in cytosolic cytochrome c in the SH/A rats compared to WKY/A and SH/V (two-way ANOVA; $p<0.05$). Outcomes indicate that ADHD individuals treated with stimulants may experience striatal mitochondrial dysregulation as adults that may be manifested behaviorally as early-stage PD.

Disclosures: A.L. Persons: None. **R. Romay-Tallon:** None. **A. Brown:** None. **T. Napier:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.23/C99

Topic: C.03. Parkinson's Disease

Support: Aligning Science Across Parkinson's (ASAP) Collaborative Research Network

NIH Grant HG005031
NIH Grant NS003134

Title: Investigating the impact of ATP10B loss of function in Parkinson's disease through ATP10B knockout murine models with and without GBA1 haplodeficiency

Authors: *H. M. SCHNEPS[1], T. CHEN[2], E. BENTEA[3], T.-U. HAN[4], Z. M. KHALIQ[5], E. SIDRANSKY[6], V. BAEKELANDT[3], P. VANGHELUWE[7];
[1]Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD; [2]NIH, North Potomac, MD, ; [3]Neurosciences, KU Leuven, Lab. for Neurobio. and Gene Therapy, Leuven, Belgium; [4]NIH/NIDCD, Rockville, MD; [5]Natl. Inst. of Neurolog. Disorders and Stroke, NIH/ NINDS, Bethesda, MD; [6]NHGRI, NIH, Bethesda, MD; [7]Cell. and Mol. Med., KU Leuven, Leuven, Belgium

Abstract: Only 30% of genetically-linked Parkinson's disease (PD) cases are connected to known genetic risk factors. Loss-of-function variants in *ATP10B*, which encodes an endolysosomal glucosylceramide (GluCer) flippase, have been identified as potential PD risk factors. Pathogenic variants in *GBA1*, the most common genetic PD risk factor, reduce levels and activity of the lysosomal enzyme glucocerebrosidase (GCase). Both *ATP10B* and *GBA1* impact lysosomal GluCer levels, potentially implicating glycosphingolipid accumulation in the development of PD. To understand the pathophysiological underpinnings of *ATP10B* mutations in PD, we evaluated murine models with (1) *Atp10b* knockout (*Atp10b*$^{(-/-)}$) and, given the genes' overlapping functions, (2) *Atp10b* knockout with *Gba1* haploinsufficiency (*Atp10b*$^{(-/-)}$/*Gba1*$^{(+/-)}$). Preliminary immunohistochemical results in 12-month-old *Atp10b*$^{(-/-)}$ mice demonstrated increased expression of astrocytic (GFAP) and microglial (Iba1, CD68) markers in the substantia nigra (SN), indicative of gliosis. Myelin basic protein and the presynaptic proteins synaptophysin and synapsin-1 were also increased in the SN. However, *Atp10b*$^{(-/-)}$ mice did not show an overt motor phenotype, even with *Gba1* haploinsufficiency, nor did they exhibit differences in the number of SN dopamine neurons or levels of striatal dopaminergic innervation. Ongoing experiments in the two models include evaluation of cellular excitability and synaptic function of GABAergic and dopaminergic SN neurons in *ex vivo* brain slices, lysosomal markers (LAMP1), GluCer, and GCase enzyme levels and activity. Future experiments will evaluate and compare markers of dopaminergic signaling dysfunction (tyrosine hydroxylase, dopamine transporter, dopamine metabolites), neuroinflammation, and α-synuclein accumulation between models, as well as the impact of aging on phenotypes in 19-month-old *Atp10b*$^{(-/-)}$ mice.

Disclosures: H.M. Schneps: None. **E. Bentea:** None. **T. Han:** None. **Z.M. Khaliq:** None. **E. Sidransky:** None. **V. Baekelandt:** None. **P. Vangheluwe:** None.

Poster

PSTR016: Parkinson's Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.24/C100

Topic: C.03. Parkinson’s Disease

Title: Transgenic mouse model of Parkinsonism Dystonia type PKDYS2

Authors: *R. ALKHATER[1], N. STEINER[2], H. FIUMELLI[3], P. J. MAGISTRETTI[4];
[1]Johns Hopkins Aramco Healthcare-KAUST, Dhahran, Saudi Arabia; [2]Dept. of Physiol., Lausanne, Switzerland; [3]Biol. and Envrn. Sci. & Engin. Div., KAUST, Thuwal, Saudi Arabia; [4]BESE, King Abdullah Univ. of Sci. and Technol., Thuwal, Saudi Arabia

Abstract: Transgenic mouse model of Parkinsonism Dystonia type PKDYS2Reem Alkhater [1,2], Nadia Steiner [1], Fathia Ben Rached[1], Hubert Fiumelli[1] and Pierre J. Magistretti[1]
1King Abdullah University of Science and Technology (KAUST), Biological and Environmental Science and Engineering (BESE), Thuwal, Saudi Arabia.2 Johns Hopkins Aramco Healthcare (JHAH), Department of Pediatrics, Dhahran, Saudi Arabia.Parkinson's Disease (PD) is the second-most common neurodegenerative disease. While it usually affects adults in their 60’s, many forms of inherited and young onset Parkinsonism start showing symptoms between ages of 14 and 40 years. Parkinsonism Dystonia Type 2 (PKDYS2) is one of the inherited forms of parkinsonism, characterized by an infantile parkinsonism phenotype. This disorder was first identified through a mutation in the *SLC18A2* gene, which causes the P387L substitution, leading to impaired vesicular monoamine transporter 2 (VMAT2) function. VMAT2 is essential for the storage and release of monoamines such as dopamine and serotonin during synaptic transmission. Patients with PKDYS2 typically exhibit global developmental delays, dystonia, and autonomic dysfunction. This characterization is documented in OMIM 618049 and was detailed by Rilstone et al. NEJM, 2013. Over the past decade, additional *SLC18A2* mutations have been identified that contribute to a broad spectrum of phenotypes and variable responses to treatment (Saida et al., 2023; Zhai et al., 2023). In exploring the molecular foundations of neurodevelopmental diseases, transgenic animal models have proven invaluable. We successfully developed the first viable transgenic mouse model for PKDYS2, providing novel insights into the consequences of VMAT2 dysfunction. We are completing the behavioral characterization of this animal model. In initial observations, we find a clear motor and coordination deficit in the homozygous mice compared to WT littermates. We also observe paradoxical events that could represent the dystonic storms seen in patients with PKDYS2. This study not only elucidates the role of VMAT2 in maintaining monoamine homeostasis and the pathophysiologic pathways that lead to the disorder but also paves the way for potential therapeutic strategies. By detailing how various *SLC18A2* mutations disrupt neurological function our findings provide a bedrock for future research and potential treatments, offering new hope for managing Parkinson’s Disease and related conditions.

Disclosures: R. Alkhater: None. **N. Steiner:** None. **H. Fiumelli:** None. **P.J. Magistretti:** None.

Poster

PSTR016: Parkinson’s Disease: Molecular and Genetic Studies

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.25/C101

Topic: C.03. Parkinson's Disease

Support: ASAP Grant

Title: Co-pathologies and immune cell activation in a model of Parkinson's Disease

Authors: *J. WEBSTER[1], Y.-T. YANG[2], N. CORBIN-STEIN[2], A. ZANE[1], L. HAMPTON[3], W. HIRST[4], J. KORDOWER[5], A. S. HARMS[2];
[1]Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; [2]Dept. of Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; [3]Biogen, Cambridge, MA; [4]DeCapo Brainscience, Cambridge, MA; [5]Arizona State Univ., Gilbert, AZ

Abstract: Lewy pathology due to alpha-synuclein (α-syn) inclusions is one of th major hallmarks of Parkinson's Disease (PD). β-Amyloid (Aβ) and phosphorylated tau (p-tau), pathologies usually found in Alzheimer's Disease (AD), have also been implicated in PD, with over 50% of patients exhibiting the co-expression of these proteins (co-pathologies). In PD postmortem tissue, neuroinflammation - the activation of glia and resident macrophages, and the infiltration of immune cells from the periphery, including T cells and monocytes - are hypothesized to be drivers of neurodegeneration. In AD cases, with Aβ and tau pathologies, microglial activation and infiltration of immune cells from the periphery have also been observed. However, how the co-expression of these pathologies contribute to the inflammatory response and overall disease phenotype is not well known in PD. To test the hypothesis that the co-expression of pathologies drives neuroinflammation, pathology load and neurodegeneration, we developed a co-pathology rodent model of PD by stereotypically injecting α-syn pre-formed fibrils (PFFs) into the striatum, and AAV-double mutant tau virus into the entorhinal cortex, of J20 transgenic mice with Aβ pathology. We analyzed immune cell populations in the brain and periphery at 3 months post-induction (3mpi). At 3mpi and 6mpi, abnormal protein pathology, as well as behavioral phenotypes and neuronal loss, were also assessed. The co-pathology mouse model exhibits Aβ, tau and α-syn pathology, with an increased protein pathology load compared to the single pathology models. There was a robust inflammatory response, including increased microglial cell number, changes in activation markers, CD68 and TLR2 and elevated MHCII expression, a complex important for antigen presentation. This was synergistic in the co-pathology model, compared to the individual models, supporting the hypothesis that these pathologies collectively may drive the progression of disease. Future studies include blocking selective T cell subsets to determine their role in the pathogenesis.

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Poster

PSTR017: Parkinson's Disease: Clinical Trials

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.01/C102

Topic: C.03. Parkinson's Disease

Support: NINDS UH3NS103468
UH3NS129898
Devices donated by Medtronic PLC

Title: Comparison of three beta oscillation biomarkers of bradykinesia in Parkinson's disease.

Authors: *S. SCHMIDT[1], R. RODRIGUEZ CAPILLA[2], J. PETERS[1], D. A. TURNER[3], W. M. GRILL[1];
[1]Duke Univ., DURHAM, NC; [2]Duke Univ. Med. Ctr., Durham, NC; [3]Neurosurg., Duke Univ. Med. Ctr., Durham, NC

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus (GP) is the leading surgical intervention for treatment of the motor symptoms of PD. However, DBS parameters are static while treatment needs fluctuate throughout the day and with levodopa levels. With the advent of DBS devices capable of sensing, there is increased interest in adaptive DBS to tailor stimulation to the current needs of the patient. Adaptive DBS promises improved symptom management with reduced side effects. Measurable and accurate biomarkers are critical for effective adaptive control of the optimal therapy level. Therefore, we examined three potential biomarkers of akinetic/rigid symptoms in a unique cohort of 6 participants with PD with bilateral leads implanted in both the STN and GP and connected to Summit RC+S^{TM} (Medtronic PLC). We quantified beta band amplitude on each lead, beta phase locking value (PLV) between leads, and mean magnitude coherence (MS Coh) between leads. All study activities were approved by the FDA and Duke IRB and all participants provided informed consent. We first conducted 300 s recordings at quintiles of the clinical STN+GP DBS amplitude and assessed bradykinesia. Increased DBS amplitude linearly reduced bradykinesia, as measured by the average speed of hand grasps near the end of each trial for 5 of 6 participants ($p < 0.05$, Pearson correlation). Further, we observed significant linear correlations between the speed of hand grasps and beta amplitude, PLV, and MS Coh in the 5 participants who received benefit to bradykinesia ($p < 0.05$, Pearson). These results suggest that each biomarker has the potential to encode the level of bradykinesia. Candidate biomarkers must also be evaluated during periods of changing DBS amplitudes to assess artifact tolerance and appropriate settling time. Therefore, we quantified biomarkers while randomly changing STN+GP DBS amplitudes without consideration of symptom level. We observed very high levels of correlation between DBS amplitude and beta amplitude, PLV, and MS Coh ($p > 0.05$, Pearson) suggesting that all biomarkers could be measured in the 10 s windows between changes in DBS amplitude. However, correlations between biomarkers and DBS amplitudes were greater than those between biomarkers and bradykinesia. This suggests that at least part of the correlation between biomarker and bradykinesia is due to the correlation to DBS amplitude. Analysis methods are needed to separate accurately the dependence on DBS amplitude, but beta amplitude, PLV, and MS Coh are promising biomarkers of bradykinesia in patients with PD.

Disclosures: S. Schmidt: None. **R. Rodriguez Capilla:** None. **J. Peters:** None. **D.A. Turner:** None. **W.M. Grill:** None.

Poster

PSTR017: Parkinson's Disease: Clinical Trials

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.02/C103

Topic: C.03. Parkinson's Disease

Support: NINDS Grant UH3NS103468
NINDS Grant UH3NS129898
Devices donated by Medtronic PLC

Title: Frequency response of dual-target deep brain stimulation (DBS) in participants with Parkinson's disease (PD)

Authors: *R. RODRIGUEZ CAPILLA[1], J. PETERS[2], H.-J. LEE[2], S.-C. CHOW[2], W. M. GRILL[2], D. A. TURNER[3], S. L. SCHMIDT[4];
[1]Duke Univ. Med. Ctr., Durham, NC; [2]Duke Univ., Durham, NC; [3]Neurosurg., Duke Univ. Med. Ctr., Durham, NC; [4]Biomed. Engin., Duke Univ., DURHAM, NC

Abstract: DBS is an effective surgical treatment for PD. By targeting the subthalamic nucleus (STN) or the globulus pallidus (GP), DBS manages primary symptoms (e.g. bradykinesia), but residual symptoms remain and side effects may be evoked. We have previously shown that STN and GP (dual target, DT) DBS was effective within a cohort of 6 PD patients. Common practice for single region DBS is to use a frequency of 130Hz, however the frequency response of DT DBS remains unknown. We studied six human participants with PD who were treated with DT DBS. We quantified the effect of stimulation frequency during DT DBS using the Medtronic Summit RC+S^{TM} implantable pulse generator. All study activities were approved by the FDA and Duke IRB and all participants provided informed consent. We conducted two sets of experiments to determine the relationship between the frequency of DT DBS, upper limb bradykinesia, and beta power. In the first experiment, we applied DT DBS at 50, 75, 100, and 125Hz and measured bradykinesia. We confirmed that bradykinesia, measured by the average speed of hand grasps, was linearly correlated with the power of the beta oscillations (13-30Hz) in the contralateral STN. Four out of the six participants exhibited significant correlation ($p < 0.05$) between hand grasp speed and beta power in the contralateral STN (max R^2 0.189 - 0.278). Faster grasp speeds corresponded to trials of 125 and 100Hz, while the absence of DBS led to lower grasp speeds. We then conducted random frequency experiments in which the frequency of DBS (2-125Hz) changed every 10s. For these experiments, we used either DT DBS or single region DBS. The LFP was recorded and analyzed to quantify beta power (Welch's method). We observed a significant reduction of beta power with each increase in DBS frequency (mean [95% CI], -0.832 [-1.247 -0.417] dB per 12.3 Hz). As well, DT DBS reduced beta power to a greater degree than single region DBS (-2.673 [-4.218 -1.129] dB). Combined, these data indicate that DT DBS can better treat bradykinesia and reduce beta power than single region DBS. Further, high frequency DBS reduced beta power and bradykinetic symptoms more effectively than low frequency DBS.

Disclosures: **R. Rodriguez Capilla:** None. **J. Peters:** None. **H. Lee:** None. **S. Chow:** None. **W.M. Grill:** None. **D.A. Turner:** None. **S.L. Schmidt:** None.

Poster

PSTR017: Parkinson's Disease: Clinical Trials

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.03/C104

Topic: C.03. Parkinson's Disease

Title: Spinal cord stimulation improves gait velocity and step length in a patient with Parkinson's disease associated gait abnormalities

Authors: *J. SLACK, A. P. YADAV;
The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Spinal cord stimulation (SCS) is an emerging technology for the treatment of Parkinson's disease (PD) associated gait abnormalities. Although SCS is shown to improve freezing of gait (FOG), its impact on specific gait features is unknown, which limits identification of SCS parameters that maximize its therapeutic effect. In this study, we employed full-body motion capture (MoCap) to study the effects of multiple SCS programs on gait in a PD patient undergoing straight-line walks (SLWs) before and after implantation of a spinal percutaneous lead. During evaluations, the subject was outfitted with 17 inertial measurement units (IMUs) from Perception Neuron (PN) which streamed real-time data to PN's Axis Studio. MoCap data was collected while the patient performed six ~7m SLWs pre-surgery and 3 days post-surgery with or without the delivery of SCS across multiple stimulation programs. SCS programs ranged from low to high frequency along with a control paradigm pre-programmed by the manufacturer. During the 3-day period between evaluations the patient received continuous SCS at the control settings. Gait analysis was performed in Python using data recorded from left and right calf sensors. Three gait features of interest, velocity, cadence, and step length were calculated by extracting steps which corresponded to peaks in the angular velocity. Velocity and step length were calculated as the ratio of total distance traveled over total elapsed time and total steps taken, respectively, during a SLW. Cadence was the ratio of total steps over total elapsed time. Stick decomposition of the thigh, calf, and foot sensors was performed in MATLAB to provide visualization of gait changes. Statistical significance was performed in GraphPad Prism on gait features averaged across SLWs by one-way ANOVA with multiple comparisons. As expected, SCS dramatically reduced FOG episodes when compared to OFF SCS condition. We also observed that SCS significantly improved velocity across all tested SCS programs when compared to pre-surgery (0.6173 ± 0.0521 m/s) with the best program (0.7806 ± 0.0501 m/s) demonstrating a 26.45% increase ($p<0.001$). Similarly, increased step length from pre-surgery (0.4080 ± 0.0511 m) were observed for three of the programs with the best program (0.5652 ± 0.0747 m) providing a 38.53% increase ($p<0.001$). Finally, significant increase in velocity in the OFF SCS condition between pre- and post-surgery (0.7402 ± 0.0555 m/s) was observed ($p<0.001$), suggesting a chronic effect of stimulation. Given the significant gait improvements

observed across all SCS programs, we postulate that SCS can become a viable treatment option for PD-associated gait issues.

Disclosures: J. Slack: None. **A.P. Yadav:** None.

Poster

PSTR017: Parkinson's Disease: Clinical Trials

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.04/C105

Topic: C.03. Parkinson's Disease

Support: UH3NS107709

Title: Neural adaptive deep brain stimulation for gait impairment and freezing of gait in Parkinson's disease

Authors: *C. CUI[1], J. CHOI[1], S. KARJAGI[1], K. B. WILKINS[1], A. S. GALA[1], C. CASSELTON[1], A. NEGI[1], P. AKELLA[1], T. HOWARD[1], L. PARISI[1], A. ABAY[1], J. A. HERRON[2], H. BRONTE-STEWART[1,3];
[1]Neurol. & Neurolog. Sci., Stanford Univ., Stanford, CA; [2]Dept. of Neurolog. Surgery, Univ. of Washington, Seattle, WA; [3]Department of Neurosurgery, Stanford University, Stanford, CA

Abstract: Background: Gait impairment and freezing of gait (GI&FOG) is a debilitating symptom of Parkinson's disease (PD) that is often refractory to medication. Exaggerated beta activity within the subthalamic nucleus (STN) is associated with both worse gait and freezing behavior in PD. Previous studies have explored the feasibility of beta-driven adaptive Deep Brain Stimulation, primarily through externalized leads or PC-in-the-loop systems. While these methods have offered high-quality signal acquisition and advanced computational capabilities for biomarker analysis, their utility is generally confined to research settings. Our study aims to investigate the adaptive DBS for GI&FOG using embedded close loop capability of Percept PC, an FDA approved sensing neurostimulator. **Method**: Two individuals with PD (one male, one female) who are implanted with the Percept PC with bilateral STN leads (Medtronic 3389) were enrolled in this study. Initial calibration and programming were performed to determine patient-specific sensing and adaptive parameters, involving measurements of STN local field potentials (LFPs) and gait kinetics and/or kinematics across various stimulation settings. These parameters were incorporated into a beta power driven dual threshold control policy. Patients then underwent blinded randomized gait testing and MDS-UPDRS assessments during adaptive DBS and continuous DBS with patient clinical settings, and also OFF-DBS. **Results**: We were able to find safe and tolerable adaptive DBS settings for both participants. Preliminary data shows that aDBS improved gait compared to OFF DBS and demonstrated comparable or superior efficacy to their optimized clinical settings. Notably, the distinct adaptive control policies between the two participants underscore the necessity of careful calibration, taking into account the potential beta modulation by resting and movement states and presence of artifacts. **Conclusion**: Our

study demonstrated feasible implementation of patient-specific adaptive therapy for GI&FOG in PD patients using the embedded capability of the implanted sensing neurostimulator. The knowledge we gained from in-lab assessments will facilitate the development of adaptive DBS for long-term at-home use.

Disclosures: C. Cui: None. **J. Choi:** None. **S. karjagi:** None. **K.B. Wilkins:** None. **A.S. Gala:** None. **C. Casselton:** None. **A. Negi:** None. **P. Akella:** None. **T. Howard:** None. **L. Parisi:** None. **A. Abay:** None. **J.A. Herron:** None. **H. Bronte-Stewart:** None.

Poster

PSTR017: Parkinson's Disease: Clinical Trials

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Program #/Poster #: PSTR017.05/C106

Topic: C.03. Parkinson's Disease

Support: NIH UG3NS128150

Title: Neuroimaging-guided optimization of deep brain stimulation lead placement and configuration for the nucleus basalis of meynert

Authors: *K. B. WILKINS[1], C. CASSELTON[2], A. ABAY[2], T. HOWARD[2], R. CROCKETT[3], M. M. ZEINEH[4], V. BUCH[5], H. BRONTE-STEWART[2];
[1]Dept. of Neurol. and Neurolog. Sci., Stanford Univ., Palo Alto, CA; [2]Dept. of Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA; [3]Univ. of Oxford, Oxford, United Kingdom; [4]Radiology, Stanford Univ., Stanford, CA; [5]Neurosurg., Stanford Univ., Palo Alto, CA

Abstract: The therapeutic efficacy of deep brain stimulation (DBS) relies on accurate lead placement and optimal stimulation parameters. The growing prevalence of high-quality neuroimaging data and improved modeling of DBS offers the potential to automate DBS parameter configuration to maximally hit a target of interest. The goal of this project was to create a neuroimaging-guided pipeline for optimizing lead placement and stimulation parameters for DBS of the Nucleus Basalis of Meynert (NBM) in Parkinson's disease (PD) for cognition. Preoperative neuroimaging data, including T1-weighted and diffusion scans, were used to define anatomical regions of interest (ROIs), including the NBM and its lateral tract. A neurosurgeon planned multiple trajectories for lead placement based on these ROIs in Brainlab Elements neuronavigational software. Based on the proposed trajectory and lead placement, the investigational Boston Scientific software Illumina was used to model the optimal stimulation configuration for maximizing overlap between the stimulation field model (SFM) and the target. Illumina was run under various constraints, including different surgical targets, additional regions of avoidance (ROAs), and various weightings of different parameters such as the weighting between maximizing ROI SFM overlap and minimizing ROA overlap. Detailed analysis of overlap with certain subsections of ROIs was carried out in the X, Y, and Z directions. We implemented this pipeline in an individual with PD who previously underwent

DBS of the subthalamic nucleus. The neurosurgeon mapped multiple trajectories for the NBM and its lateral tract. Different trajectories were used depending on the target of interest, which resulted in different stimulation configurations and ensuing SFMs. The added constraint of additional ROAs resulted in smaller stimulation amplitudes and SFMs. Additionally, tunable Illumina parameters, such as the weighting between ROI and ROA overlap, altered the stimulation configuration. Subsection analysis of ROIs allowed more detailed comparisons of different SFMs to more directly compare overlap in the X, Y, and Z direction. The proposed novel pipeline allows for anatomy-guided placement of DBS leads and subsequent automation of initial stimulation configurations. This could facilitate clinical programming for new indications, such as DBS for cognition, where acute stimulation-induced behavioral effects cannot be used to guide programming. The feasibility of this approach will be assessed in an upcoming pilot clinical trial of NBM DBS in PD.

Disclosures: K.B. Wilkins: None. **C. Casselton:** None. **A. Abay:** None. **T. Howard:** None. **R. Crockett:** None. **M.M. Zeineh:** None. **V. Buch:** None. **H. Bronte-Stewart:** None.

Poster

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Program #/Poster #: PSTR017.06/C107

Topic: C.03. Parkinson's Disease

Support: NIH UG3NS128150
NIH P30AG066515

Title: Exploring the cognitive-motor syndrome in progressive neurodegenerative diseases

Authors: *A. K. ABAY[1], C. CASSELTON[1], T. HOWARD[1], K. B. WILKINS[1], G. SEO[1], R. CROCKETT[2], S. KARJAGI[1], A. NEGI[1], C. CUI[1], **H. BRONTE-STEWART**[1];
[1]Stanford Univ., Stanford, CA; [2]Univ. of Oxford, Oxford, United Kingdom

Abstract: Cognitive impairment in progressive neurodegenerative diseases such as Parkinson's Disease (PD) and Dementia of Lewy Bodies (DLB) is partially linked to degeneration of the brain's cortical cholinergic network; the hub of this network is the Nucleus Basalis of Meynert (NBM). Although the NBM and cholinergic network are affected in early stages of PD, cognitive impairment is not usually clinically evident until later stages of disease and cognitive rating scales are not well suited to detect nor predict cognitive impairment. There are aspects of gait and fine motor control (such as speed and variability) that correlate with cognitive impairment, and have been demonstrated to be better predictors of cognitive decline. This is termed the cognitive-motor syndrome. In this study, we assessed motor and cognitive correlates of cholinergic network degeneration in DLB and PD with mild cognitive impairment (MCI), compared to age-matched healthy controls (HC). We recruited 18 participants, equally divided into cohorts of: clinically established PD with MCI, clinically established DLB, and HC.

Participants underwent motor testing, computerized cognitive testing, and a neuropsychological battery to assess motor and cognitive symptoms. Motor testing included a stepping-in-place task, measuring gait variability, and a repetitive alternating finger tapping task, measuring fine motor control. Computerized cognitive testing included the Continuous Temporal Expectancy Task and Sustained Attention Task. These measured top-down and bottom-up processing, respectively; both are modulated by the brain's cholinergic network. The neuropsychological battery provided both a large-scale measure of cognition, and domain-specific measures for executive functioning, visuospatial processing, memory formation, attention, language and mood. Correlations of motor and cognitive function will be presented and compared among cohorts. This three-pronged approach of motor, cholinergic-specific cognitive, and general cognitive assessment will help characterize cholinergic deficits across PD-MCI and DLB. The results of this study will shed light on the cognitive-motor syndrome across neurodegenerative diseases.

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Poster

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Program #/Poster #: PSTR017.07/C108

Topic: C.03. Parkinson's Disease

Support: NIH UG3NS128150
P30AG066515

Title: Examining the degeneration of the nucleus basalis of meynert across different severities of mild cognitive impairment

Authors: *C. CASSELTON[1], K. B. WILKINS[1], T. HOWARD[1], A. ABAY[1], R. CROCKETT[2], A. NEGI[1], G. SEO[1], H. BRONTE-STEWART[1];
[1]Stanford Univ., Stanford, CA; [2]Univ. of Oxford, Oxford, United Kingdom

Abstract: IntroductionThe Nucleus Basalis of Meynert (NBM) is the hub of the cortical cholinergic network and is affected in neurodegenerative diseases such as Alzheimer's disease (AD). NBM degeneration has been linked to the deterioration in cognitive performance. The steppingstone between normal cognitive aging and AD is mild cognitive impairment (MCI). MCI can be classified based on severity, mild or moderate, at the time of diagnosis. Mild MCI has been associated with a reduced risk of progression to AD or dementia relative to moderate MCI. However, there is still a lack of clarity about the differences between the two diagnoses; some mild MCI patients can still develop AD or dementia, or no longer be diagnosed with MCI altogether. Determining the structural differences of the NBM between mild MCI and moderate MCI might shed light on the differences that lead to progression to AD. MethodsPreliminary

analysis consisted of 20 participants; 10 mild MCI and 10 moderate MCI, data were extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The ADNI database had the two cohorts labelled as early MCI and late MCI, which we refer to as mild MCI and moderate MCI. Mild MCI and moderate MCI diagnoses were determined using the Wechsler Memory Scale Logical Memory II scores. Participants' earliest viable T1 magnetic resonance imaging scans were selected. The scans were quality checked and the grey matter volume of the NBM was analyzed through voxel-based morphometry using the SPM12 software. NBM volumes were then compared between groups.ResultsAlthough preliminary analysis contained a small sample size, a slight decrease in mean NBM volume in the moderate MCI group (0.22 ± 0.039) compared to the mild MCI group (0.23 ± 0.039) was found. Considering the preliminary results, further analysis with an increased sample size will be done to increase statistical power. Future analysis will analyze the fractional anisotropy and mean diffusivity of the NBM white matter bundles to determine differences in degeneration of the NBM's major tracts.
ConclusionThe preliminary results of this study show that there is a decrease in NBM volume for the moderate MCI group compared to mild MCI. Further analysis, including the white matter bundles of the NBM, will shed light on the structural brain differences between mild MCI and moderate MCI groups. NBM degeneration could possibly determine whether mild MCI and moderate MCI are differing groups or moderate MCI is the same as mild MCI, but has not been recognized in a timely manner.

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Poster

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Program #/Poster #: PSTR017.08/C109

Topic: C.03. Parkinson's Disease

Support: NIH UH3NS107709

Title: Kinematic adaptive deep brain stimulation for gait impairment and freezing of gait in Parkinson's Disease

Authors: *S. KARJAGI[1], Y. KEHNEMOUYI[2], L. PARISI[3], P. AKELLA[3], E. LAMBERT[3], J. MELBOURNE[4], A. S. GALA[3], C. CUI[5], J. O'DAY[2], K. B. WILKINS[3], M. N. PETRUCCI[2], S. ADITHAM[3], G. ORTHLIEB[3], J. A. HERRON[6], H. BRONTE-STEWART[7];
[1]Neurol., Stanford Sch. of Med., Stanford, CA; [2]Bioengineering, Stanford Univ., Stanford, CA; [3]Neurol., Stanford Univ., Stanford, CA; [4]Stanford, Stanford Univ., Stanford, CA; [5]Dept. of Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA; [6]Dept. of Neurolog. Surgery, Univ. of Washington, Seattle, WA; [7]Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA

Abstract: Parkinson's disease (PD) manifests complex yet episodic and predictable gait impairment (GI), characterized by slow movements, arrhythmic stepping, and severe episodes of freezing of gait (FOG). Traditional deep brain stimulation (DBS) effectively treats GI&FOG to some degree but employs constant amplitude and frequency in an open-loop (ol) configuration, failing to adapt to these episodic and predictable variations in symptom severity. To address this limitation, this study evaluated the safety, tolerability, and efficacy of two Kinematic adaptive (Ka) DBS algorithms. The first algorithm utilized a validated logistic regression model to predict the probability of freezing of gait *(P(FOG))* from data captured by inertial measurement units (IMUs) on the participant's shanks. The output, *P(FOG)*, directly informed real-time adjustments in DBS intensity or frequency based on predefined thresholds. The second algorithm used a single-threshold gait arrhythmicity model as a surrogate for *P(FOG)*, using arrhythmicity as a kinematic control variable for KaDBS. Eight participants with PD, implanted with the Medtronic Summit™ RC+S system, performed gait tasks under various DBS configurations including OFF DBS therapy, olDBS, KaDBS, and random intermittent (i) olDBS. The KaDBS algorithms adjusted the stimulation either by varying the amplitude or by switching between high and low frequencies (140 Hz to 60 Hz). Safety and tolerability were assessed through participant feedback questionnaires, and quantified gait parameters and freezing behaviors with kinematic data from shank IMUs. Participants consistently reported no adverse effects related to adjustments in KaDBS intensity or frequency during testing. The evaluation of the second KaDBS algorithm, which enabled dynamic adjustments in DBS intensity, was conducted across four conditions (OFF DBS, KaDBS, olDBS, and iolDBS). Using a linear mixed-effects model significant condition effects were observed on percentage time freezing ($F=5.99$, $p=0.0041$), arrhythmicity ($F=3.85$, $p=0.027$), and shank angular velocity ($F=4.09$, $p=0.021$). Following FDR correction, pairwise comparisons revealed significant improvements in these metrics when comparing from OFF DBS to KaDBS (all $p<0.05$). This study demonstrated that KaDBS significantly improved GI&FOG in PD by dynamically adjusting stimulation intensity and frequency based on real-time measures of gait arrhythmicity and the *P(FOG)*, offering a targeted and responsive therapeutic approach.

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Poster

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.09/C110

Topic: C.03. Parkinson's Disease

Support: NINDS UH3NS107709

Title: Sixty-hertz beta-burst driven adaptive deep brain stimulation for freezing of gait in Parkinson's disease

Authors: *A. S. NEGI[1], K. B. WILKINS[1], C. CUI[1], E. LAMBERT[1], J. MELBOURNE[1], M. N. PETRUCCI[1], S. ADITHAM[1], G. ORTHLIEB[1], A. S. GALA[1], P. AKELLA[1], L. PARISI[1], J. A. HERRON[2], H. BRONTE-STEWART[1];
[1]Neurol. and Neurolog. Sci., Stanford Sch. of Med., Palo Alto, CA; [2]Dept. of Neurolog. Surgery, Univ. of Washington, Seattle, WA

Abstract: Introduction: Gait impairment and freezing of gait (GI&FOG) are debilitating symptoms of Parkinson's disease (PD). Continuous deep brain stimulation (cDBS) can improve FOG; however, its efficacy wanes in advanced stages of PD. In some people with PD, low-frequency cDBS has demonstrated more efficacy than high-frequency cDBS for GI&FOG. Neural adaptive DBS (NaDBS) adjusts stimulation amplitude in response to the amplitude and duration of fluctuations (bursts) of local field potential power in the 13-30 Hz range (beta band) and has been shown to be efficacious in PD at high frequency. In this study, we tested the safety and feasibility of 60 Hz NaDBS for GI&FOG in PD. Methods: 8 individuals with PD were implanted with the investigational Summit^{TM} RC+S (Medtronic, PLC) in the subthalamic nucleus. Gait tasks (harnessed Stepping in Place (SIP) and the free walking Turning and Barrier Course (TBC)), overall motor impairment, and bradykinesia were evaluated in a double blinded fashion OFF DBS and during cDBS, randomly adapting intermittent DBS (iDBS), and NaDBS at 60 Hz stimulation. Safety and tolerability questionnaires were administered after each assessment. Results: Five participants found 60 Hz NaDBS to be safe and tolerable. In these participants, the NaDBS controller successfully adapted on 60 Hz parameters. In the SIP task, three out of five participants experienced improvements in gait impairment and/or FOG on 60 Hz NaDBS relative to OFF DBS, with comparable performance to 60 Hz cDBS. In a TBC gait task, two out of four participants experienced improvements in gait impairment and/or FOG on 60 Hz NaDBS relative to OFF DBS, with comparable performance to cDBS. For three participants, a tolerable, therapeutic stimulation intensity with 60 Hz cDBS could not be found due to tremor in two participants and lack of control of other PD symptoms in one participant, resulting in discontinuation of further testing. Discussion: 60 Hz NaDBS was safe and tolerable in majority of participants and improved GI&FOG in a subset of these. Three out of eight participants were unable to tolerate 60 Hz NaDBS due to insufficient control of other PD symptoms during 60 Hz cDBS. This demonstrates that low-frequency NaDBS may be efficacious for GI&FOG but may result in emergent tremor for tremor-dominant individuals.

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Poster

PSTR017: Parkinson's Disease: Clinical Trials

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Program #/Poster #: PSTR017.10/C111

Topic: C.03. Parkinson's Disease

Support: NIH UH3NS107709
NIH UG3NS128150

Title: Subthalamic Nucleus Beta Desynchronization in Pre-Movement Initiation of Sit-to-Walk Task in Parkinson's Disease

Authors: *G. SEO[1], K. B. WILKINS[2], H. BRONTE-STEWART[3];
[1]Stanford Univ., Stanford, CA; [2]Neurol., Stanford Univ., Palo Alto, CA; [3]Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA

Abstract: Sit-to-walk is a complex motor task that involves balance, postural control, and coordinated execution of movements which commonly deteriorate in individuals with Parkinson's disease (PD). The exaggerated beta-band oscillatory activity in the subthalamic nucleus (STN) has been identified as a biomarker for motor impairment in PD. While the previous research has mainly centered on the resting and movement states, neural activity in the STN during the movement planning and movement initiation period have been less explored. This study aims to characterize local field potential power (LFP) in the beta (13-30 Hz) range in STN during the preparatory-initiation phase of a sit-to-walk task. The study further investigates the connection between movement initiation-related neural activity and the severity of exhibited gait impairment in PD. Four participants with PD, implanted with a sensing deep brain stimulation (DBS) system with an embedded 3-axis accelerometer (Medtronic Summit™ RC+S), performed externally cued sit-stand-walk tasks off medication and OFF DBS. Accelerometer data and LFP were recorded simultaneously via the DBS system. The movement onset was marked based on the angular acceleration of the chest where the accelerometer of the DBS system was located. The beta power (13-30 Hz) of STN LFP, normalized by the seated-resting period beta power, was calculated pre- and post-movement onset (initiation of sit-to-stand and stand-to-walk, respectively). The pre-movement onset beta power and the difference in the beta power between pre- and post-movement onset were then compared to each participant's MDS-UPDRSIII posture- and gait-related subscores. The preliminary results demonstrated beta power decreased (beta desynchronization) in either one or both STNs during the pre-movement initiation period for all PD participants. Furthermore, the severity of posture- and gait-related motor impairment, as indicated by MDS-UPDRS III subscores, was associated with a greater decrease in pre-movement onset beta power. The MDS-UPDRS III subscores were also related to a greater difference in beta power between pre- and post-movement onset. These findings suggest a possible role for beta desynchronization during movement preparation as an indicator for postural instability and gait impairment in Parkinson's disease. Additionally, taking into account the fluctuations in beta power around the period of movement onset of sit-to-walk could contribute to the development of a more robust beta-driven adaptive DBS system, optimized for each individual with PD to enhance gait function.

Disclosures: G. Seo: None. **K.B. Wilkins:** None. **H. Bronte-Stewart:** None.

Poster

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Topic: C.03. Parkinson's Disease

Support: ADRC Grant P30AG066515
NBM Grant UG3NS128150

Title: Characterizing the structural integrity of the NBM and its projections in neurodegenerative disease

Authors: *T. HOWARD[1], K. B. WILKINS[2], R. CROCKETT[3], A. ABAY[1], C. CASSELTON[4], J. MELBOURNE[2], H. BRONTE-STEWART[4];
[1]Stanford Univ., Stanford, CA; [2]Neurol., Stanford Univ., Palo Alto, CA; [3]Univ. of Oxford, Oxford, United Kingdom; [4]Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA

Abstract: Recent research has demonstrated that degeneration of the cholinergic network could bepartially responsible for the decline in cognitive function found in Alzheimer's Disease (AD) andParkinson's Disease (PD). Some aspects of cognitive functioning that have been shown to beaffected are attention, visuospatial processing, and arousal. The goal of this study was todetermine the structural integrity of the Nucleus Basalis of Meynert(NBM), also known as thecortical cholinergic hub, and its projections, in people in different stages of AD, PD, and PD-MCI(mild cognitive impairment). This was also determined in age-matched healthy controls.We collated data from 250 participants: 50 healthy controls (HC), 50 AD-Mild CognitiveImpairment (AD-MCI), 50 AD, 50 PD-no MCI, and 50 PD-MCI. We used two different databases:Parkinson's Progression Markers Initiative and the Alzheimer's Disease Neuroimaging Initiativewhich included both structural MRIs and neuropsychological batteries. We assessed graymatter volume of the NBM from the T1 image across each of these groups using voxel-basedmorphometry. For the tract analysis, we extracted the mean diffusivity of the lateral and medialNBM tracts using diffusion tractography.Preliminary analyses showed that the mean NBM volume for the AD-MCI cohort was lowerthan that of the HC cohort. The PD-MCI cohort showed a lower NBM volume than the PD-noMCI cohort. According to tractography analysis, there was an increase in mean diffusivity forboth tracts from HC to MCI to AD, reflecting a loss of integrity of these white matter bundles. Therewas also an increase in mean diffusivity for both tracts for PD-MCI when compared to the PDcohort. Future analysis will investigate the relationship between observed degeneration andneuropsychological assessments.The results of this study will characterize the degeneration of the cortical cholinergic systemacross a spectrum of neurodegenerative diseases, which may lead to more targeted therapies.

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Poster

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Topic: C.03. Parkinson's Disease

Support: NIH NINDS Grant UG3NS130202

Title: Unilateral subthalamic nucleus deep brain stimulation improves patient-perceived global, motor, and mental health in people with Parkinson's disease

Authors: *S. A. BRINKERHOFF[1], F. G. ROBINSON[2], V. A. DEL BENE[2], R. C. MARTIN[2], C. L. GONZALEZ[2], M. T. HOLLAND[3], N. BENTLEY[3], H. C. WALKER[2,4,5];
[1]Neurol., Univ. of Alabama, Birmingham, Birmingham, AL; [2]Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; [3]Neurosurg., Univ. of Alabama at Birmingham, Birmingham, AL; [4]Neurosurgery, University of Alabama at Birmingham, Birmingham, AL; [5]Department of Biomedical Engineering, University of Alabama at Birmingham, Birmingham, AL

Abstract: Deep brain stimulation (DBS) addresses motor (bradykinesia, tremor, rigidity) and some nonmotor (depression, cognitive impairment, pain, sleep disturbance) symptoms from Parkinson's disease. Patient-perceived quality of life can be assessed in a cost- and time-effective manner but is relatively neglected in prior DBS studies. METHODS: 30 patients underwent unilateral subthalamic nucleus DBS and completed validated self-report inventories before surgery and at 3 post-operative visits over 2-12 months. The inventories assessed quality of life (Parkinson's disease questionnaire-8, PDQ8) and specific motor and nonmotor symptoms with PROMIS and NEURO-QoL. Linear mixed models estimated how unilateral DBS affected patient-perceived quality of life related to global, motor, and non-motor symptoms over time, accounting for baseline and individual variability. Mixed models assessed whether disease severity (MDS-UPDRS III) was related to patient-perceived outcomes. RESULTS: Changes in perceived quality of life, mental health, and feelings of stigma after DBS were strongly influenced by preoperative perceptions. Patients with the poorest preoperative scores improved in these areas, while those with higher baseline scores did not. Patient-perceived upper extremity function, sleep disturbance, cognitive function, and participation in social activities improved after DBS regardless of preoperative patient perception. MDS-UPDRS III scores 'off' medications related to better patient-perceived quality of life, physical function, upper extremity function, cognitive function, mental health, sleep quality, anxiety, social participation, and feelings of stigma. CONCLUSIONS: This study supports the utility of the NIH-validated PROMIS and NEURO-QoL instruments as efficient, comprehensive assessments for patients undergoing DBS for Parkinson's disease. While the PDQ8 proved sensitive to improvements, the additional inventories captured more nuanced changes in multidomain function. The computer adaptive nature, brief completion time (<15 minutes), and incorporation of age-based norms of PROMIS and NEURO-QoL underscore their practical value for evaluation of diverse aspects of the patient experience related to DBS.

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Poster

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Program #/Poster #: PSTR017.13/C114

Topic: C.03. Parkinson's Disease

Title: Cortical stimulation-based Transcriptome shifts on Parkinson's disease animal model

Authors: H. SHIN[1,6], *C. YOU[2,3], E. BAEG[8], J. KIM[4], S. YANG[5,7,9];
[1]Bioengineering and Nano-Bioengineering, [2]nanobio engineering, [3]Incheon Natl. Univ., Incheon, Korea, Republic of; [4]Div. of Life Sci., Incheon Natl. Univ., INCHEON, Korea, Republic of; [5]Nano-bioengineering, Incheon Natl. Univ., Incheon, Korea, Republic of; [6]Ctr. for Brain-Machine Interface, Incheon, Kosovo, Republic of; [7]Incheon Natl. Univ., Ctr. for Brain-Machine Interface, Incheon, 22012, Korea, Republic of; [8]CNIR, Inst. For Basic Sci. (IBS), Suwon, Korea, Republic of; [9]gBrain Inc., Incheon, 21984, Korea, Republic of

Abstract: Parkinson's disease is the second most prevalent neurodegenerative disorder, characterized by the degeneration of dopaminergic neurons. Significant improvements in gait balance, especially in step length and velocity, were revealed by non-invasive wireless cortical stimulation. RNA transcriptome analysis was conducted to demonstrate the cellular mechanism, specifically targeting the primary motor cortex. It was indicated by our findings that 38 differentially expressed genes, initially down-regulated following Parkinson's disease induction, were subsequently up-regulated to normal levels after cortical stimulation. As a result, 38 DEGs are proposed as a biomarker of motor disorder treatment in Parkinson's disease. These genes are implicated in crucial processes such as astrocyte-mediated blood vessel development and microglia-mediated phagocytosis of damaged motor neurons, suggesting their significant roles in improvement of behavior disorder. Moreover, these biomarkers not only facilitate rapid and accurate diagnosis of Parkinson's disease but also assist customization therapy.
Keywords: Parkinson's disease, Cortical stimulation, Transcriptome next-generation sequencing, Wireless technology, Motor function

Disclosures: H. Shin: None. **C. You:** None. **E. Baeg:** None. **J. Kim:** None. **S. Yang:** None.

Poster

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Title: Gait Parameter Changes in Parkinson's Disease Patients Receiving Adaptive Deep Brain Stimulation

Authors: *K. LOUIE[1], J. BALAKID[2], J. E. BATH[3], H. FEKRI AZGOMI[4], J. MARKS[5], P. A. STARR[6], D. D. WANG[2];
[1]Univ. California San Francisco, San Francisco, CA; [2]Univ. of California San Francisco, San Francisco, CA; [3]UCSF, LAFAYETTE, CA; [4]Neurolog. Surgery, Univ. of California San Francisco, San Francisco, CA; [5]Univ. of California, San Francisco, San Francisco, CA; [6]Univ. of California, San Francisco, Mill Valley, CA

Abstract: Gait disturbances present a significant challenge for individuals with Parkinson's disease (PD), often resistant to conventional treatments like dopamine replacement therapy and deep brain stimulation (DBS). Recently, studies recording local field potentials from free walking PD patients have shown modulations in phase with walking. These modulations might be disrupted by continuous DBS, potentially decreasing its effectiveness in addressing gait issues. Adaptive DBS (aDBS) is a new therapy designed to change stimulation parameters depending on the current need of the patient and has shown improved symptom improvements in PD patients with prominent rigidity and bradykinesia. aDBS may be used to deliver stimulation to promote the natural modulations seen during walking. In this study, we delivered personalized aDBS to two patients with PD and analyze changes in their gait parameters.Two PD patients had bilateral DBS leads implanted in the globus pallidus interna (GPi) and subdural cortical paddles overlying the primary motor (M1) and premotor (PM) cortices, all connected to the bidirectional sensing RC+S neural stimulator. Patients were brought into a gait lab to record their local field potentials (LFP) from cortical and subcortical electrodes, and gait kinematic data using external motion tracking systems, while walking back-and-forth overground for 200 steps. Biomarkers specific to contralateral leg swing were identified through a data-driven approach, utilizing LFP spectral power synchronized to each patient's gait phase. These identified biomarkers were embedded into the patient's neural stimulator for aDBS, which was then trialed to assess accuracy and observe changes in gait parameters.We found that aDBS significantly alters gait parameters compared to conventional DBS therapy. Step length and time both decreased when patients received aDBS, with an average reduction of 9 cm and 30 ms, respectively. Leg symmetry improved in both patients under aDBS, where the left and right step length and time were equal. Additionally, step length and time variance decreased under aDBS, with a more pronounced effect on Subject 2.Gait parameters were significantly different when the patient's received aDBS compared to continuous DBS. This study shows that aDBS targeted to deliver stimulation at during each gait cycle is feasible and can be used to better treat gait disturbances in people with PD.

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Poster

PSTR017: Parkinson's Disease: Clinical Trials

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.15/C116

Topic: C.03. Parkinson's Disease

Title: Medtronic Percept PC neurostimulator longevity; utilizing in-device battery estimates comparing Percept PC to previous Medtronic Activa PC and Abbott Infinity 7 PC

Authors: *E. L. HARGREAVES[1], D. L. CAPUTO[2], D. DOLCE[1], R. J. DIPAOLA[2], S. F. DANISH[1];
[1]Neurosurg., Jersey Shore Univ. Med. Ctr. (JSUMC), Neptune, NJ; [2]Neurol., Jersey Shore Univ. Med. Ctr. (JSUMC), Neptune, NJ

Abstract: Here, we examine the differences between the Permanent Cell neurostimulator longevity based on the actual longevity of Medtronic's Activa PC and Abbott's Infinity 7 PC versus Medtronic's newer Percept PC utilizing the lattermost's battery estimate. The Activa PC 37601 released in May of 2009 was promoted as having a duration of 2-5 years. In June of 2020 Medtronic received FDA approval for its Percept PC B35200, with claims that it would outlast its predecessor. Previously, we examined these claims by contrasting the longevity of 35 Activa PC implants, to their subsequent Percept PC implant battery estimates utilizing identical parameters and contact configurations, during device exchanges. Analyses stratified the device longevity by the number of exchanges. Results indicated that Percept PCs equaled their predecessors, if an initial exchange, but superseded their predecessors if tertiary exchanges. This was different than the standard decline in longevity with successive Activa PCs. Here, we now examine Medtronic's claims of Percept longevity by examining the battery estimates of initial Percept PC implants, but only after more than 9 months, when programming is presumed to be largely stable. Battery estimates were derived from 25 individuals implanted from July 2020 to June 2023. The average interval between implantation and obtaining the estimate was 1.29 years (sem= 0.12; min=9.2 months, max=24.4 months). The interval between implantation and when the estimate was obtained was summed with the estimate to produce the overall longevity estimate. The average overall longevity estimate from the 25 individuals was 6.41 years (sem=0.66). The Percept overall longevity estimate was statistically greater than the average longevity of 92 initially implanted Activa PCs (p=0.0019) which was 4.13 years (sem=0.11) and similarly greater than the average longevity of 20 initially implanted Infinity 7s (p=0.0016) which was 4.03 years (sem=0.29). To summarize, the overall longevity estimate of initially implanted Percept PCs after a minimum of 9 months of programming was greater than either of the initially implanted Activa PCs and Infinity 7 PCs, by more than 2.25 years.

Disclosures: E.L. Hargreaves: None. **D.L. Caputo:** None. **D. Dolce:** None. **R.J. DiPaola:** None. **S.F. Danish:** F. Consulting Fees (e.g., advisory boards); Medtronic.

Poster

PSTR017: Parkinson's Disease: Clinical Trials

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Program #/Poster #: PSTR017.16/C117

Topic: C.03. Parkinson's Disease

Support: NIH-1R01NS129115-01

Title: Augmented reality to quantify instrumental activities of daily living in people with Parkinson's Disease

Authors: *R. KAYA[1], A. BAZYK[1], M. MILLER KOOP[2], A. ROSENFELDT[3], C. WALTZ[4], J. L. ALBERTS[2];
[1]Cleveland Clin., Cleveland, OH; [2]Biomed. Engin., Cleveland Clin., Cleveland, OH; [3]Cleveland Clin. Fndn., Cleveland, OH; [4]Biomed. Engin., Cleveland Clin. Fndn., Cleveland, OH

Abstract: **Background:** Instrumental activities of daily living (IADLs), functional tasks that are necessary to maintain independent living (e.g., shopping, taking medication, food preparation), provide a model for quantifying cognitive and motor performance during meaningful activities in individuals with Parkinson's Disease (PD). A standardized and scalable technological approach to measuring IADL function is needed to better understand and effectively treat PD as declines in IADL capacity are considered a prodromal marker to PD. Accepted assessments of IADL function typically target a single domain of performance, i.e. cognition, therefore these assessments fail to reflect real-life IADL function. Augmented reality (AR), a technology that superimposes digital images on the user's view to enhance the real world, represents a novel and innovative solution to quantify IADL function. This project aimed to develop accurate assessments of IADL function via concurrent motor and cognitive performance using AR, and to differentiate IADL function by stage of PD severity. **Methods**: The Microsoft HoloLens 2 (Microsoft, Redmond, WA, USA) platform was used to deliver and assess performance during multiple IADL tasks, including money management and shopping. Tasks required participants to accurately count and sort money and interact with holographic vending machines to solve complex story problems. Quantitative metrics of cognitive (e.g., attention, executive function, reasoning, planning, memory) and motor functions (hand movements, balance) necessary to successfully complete the IADLs in the real world were captured. **Results:** Comparison of preliminary data from two participants, one with mild PD (age = 63; MoCA = 26; MDS UPDRS III score = 24; Hohen and Yahr (H&Y) II) and one with severe PD (age = 72; MoCA = 23; MDS UPDRS score = 51; H&Y IV) demonstrated that the individual with greater PD severity completed all IADL tasks with slower trial times (average = 75% slower), lower accuracy on the money counting tasks (0 vs 100% correct), and slower upper extremity movement velocity (0.34 cm/s vs 0.22 cm/s) . **Conclusion:** Collectively, these preliminary data demonstrate the ability of augmented reality technology to elicit and capture performance differences between varying levels of baseline motor and cognitive function in people with PD during our IADL scenarios. Success in developing engaging, ecologically valid digital tasks coupled with HL2 movement quantification capabilities indicates AR technology is a logical solution to precisely quantify PD symptoms and IADLs with a single platform technology. Data from 35 individuals with PD will be presented as part of the poster.

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Poster

PSTR017: Parkinson's Disease: Clinical Trials

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.17/C118

Topic: C.03. Parkinson's Disease

Support: Swiss national science foundation
Foundation for neurology Switzerland
Parkinson Schweiz foundation
Parkinson move foundation

Title: Neural decoding from deep brain electrodes to support closed loop therapies in Parkinson's patients

Authors: *S. SCAFA[1,2,4], R. WANG[2], P. SANCHEZ LOPEZ[2], I. SAKR[2,5], C. VARESCON[6], K. LEE[7], A. PUIATTI[4], H. LORACH[3,8,5], A. COLLOMB-CLERC[9], G. COURTINE[2,5,10], J. BLOCH[2,5,10], E. MORAUD[8,2];
[1]Univ. of Lausanne, Lausanne, Switzerland; [3]SV-BMI-UPCOURTINE, [2]Defitech Ctr. for Interventional Neurotherapies (.NeuroRestore), Lausanne Univ. Hosp. (CHUV) and Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland; [4]Inst. of Digital Technologies for Personalized Healthcare (MeDiTech), Univ. of Southern Switzerland (SUPSI), Lugano, Switzerland; [5]NeuroX Institute, Sch. of Life Sciences, Ecole Polytechnique Fédérale de Lausanne (EPFL), Geneve, Switzerland; [6].Defitech Ctr. for Interventional Neurotherapies (.NeuroRestore), Lausanne Univ. Hosp. (CHUV) and Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland; [7]Wyss Ctr. for Bio and Neuroengineering, Genève, Switzerland; [8]Dept. of Clin. Neurosciences, Lausanne Univ. Hosp. (CHUV) and Univ. of Lausanne (UNIL), Lausanne, Switzerland; [9]NeuroX Inst. (EPFL), Geneve, Switzerland; [10]Dept. of Neurosurgery, Lausanne Univ. Hosp. (CHUV) and Univ. of Lausanne (UNIL), Lausanne, Switzerland

Abstract: Despite impressive advances in neuromodulation therapies for Parkinson's disease (PD), a big majority of patients with advanced PD develop disturbances of gait and balance, including postural instability, festination, or freezing of gait, that are refractory to existing treatments. These deficits lead to frequent falls and increase comorbid conditions. Closed-loop stimulation therapies of brain and spinal cord have the potential to better address locomotor abnormalities. However, the delivery of stimulation must be tuned online to the fluctuating state of patients, as well as to task- and context-related constraints encountered in daily life. Such closed-loop therapies are contingent on biomarkers that inform about locomotor activities and deficits in real-time. Here, we aimed to leverage the neural sensing capabilities of last-generation neurostimulators for deep brain stimulation to (i) identify neural biomarkers that underlie locomotor function and dysfunction in the subthalamic nucleus of PD patients, (ii) characterize

changes in these biomarkers under different therapeutic conditions (medication, DBS), and (ii) prototype a modular decoding framework that is able to robustly predict locomotor states and deficits despite fluctuations and real-life constraints. We recorded 35 participants with advanced PD implanted with DBS, and we thoroughly characterized the changes induced by LDopa and DBS on gait biomarkers, across a variety of locomotor tasks of daily life. We found distinct modulations in low-beta, high-beta and Gamma bands that encoded locomotor states such as sitting, standing and walking. Gait encoding across these frequency bands responded differently to DBS and LDopa, which hindered the performance of a single neural decoder across different therapeutic conditions. We leveraged these observations to design a modular framework that automatically selects among two neural decoders in real-time, based on condition-specific neural correlates. This modular framework robustly coped with therapy-related fluctuations. Considering the large number of patients treated worldwide with DBS implants, as well as the capabilities of newest commercial stimulators, our work pave the way for the possibility of controlling the stimulation in closed-loop neuromodulation therapies that address gait deficits in everyday life conditions.

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Poster

PSTR017: Parkinson's Disease: Clinical Trials

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.18/C119

Topic: C.03. Parkinson's Disease

Support: Community Engagement Grant from Parkinson's Foundation to JA, MG, KN, HSB
PGRF and Nix family foundation scholarship to MMV

Title: Jumpstart your journey: Effects of a 6-week rehabilitation program on newly diagnosed individuals with Parkinson's Disease

Authors: *M. MEYER VEGA[1], J. AGRIMIS[2], M. GEORGE[2], K. NEGRETE[2], C. AMOS[3], J. HOGAN-MAGUIRE[3], K. KOVALESKI[3], P. TOLLE[3], B. WINTNER[3], N. SHAH[1], H. S. BAWEJA[1];
[1]Auburn Univ., Auburn, AL; [2]NeuroLab360, Encinitas, CA; [3]San Diego State Univ., San Diego, CA

Abstract: INTRODUCTION: Currently, there are ten million people living with Parkinson's Disease (PD) worldwide. It is characterized by motor impairments including bradykinesia, rigidity, tremor, and postural instability. These motor impairments can be detrimental to an individual's quality of life and ability to perform activities of daily living. While these

impairments can be improved with interventions such as an exercise-based rehabilitation program, there is limited evidence of their effectiveness on maintaining motor function in newly diagnosed individuals. Therefore, the purpose of our study was to investigate the effects of a 6-week multicomponent exercise rehabilitation program on individuals newly diagnosed with idiopathic PD. METHODS: Twelve participants (6 men and 6 women) underwent 6-weeks of an individualized physical therapy exercise rehabilitation program, once per week. Three participants were excluded from the analysis due to their inability to participate in the second testing session. Participants visited the clinic for two testing sessions (pre-rehab on Day 1 and post-rehab on Day 42). Outcomes measured were quality of life using the Parkinson's Disease Questionnaire-8 (PDQ-8), functional strength and endurance (30 sec sit-to-stand test), fine motor control and dexterity (9-Hole Peg test), dynamic balance and dual-task ability (MiniBEST test), static balance (3D force-plate) and gait analysis (GaitSense 2.0 treadmill). RESULTS: We found that after a 6-week program of individualized regimented: 1) All subjects showed a decline in their PDQ-8 scores and achieved higher scores in the 30 sec sit-to-stand test. 2) 67% of the participants decreased their completion time for the 9-Hole Peg test, improved their static balance with eyes closed, increased their average cadence, and increased their left stride length. 3) 56% of the subjects increased their static balance with eyes open, increased their average speed, increased their step length in both legs, and increased their right stride length. CONCLUSION: Our preliminary findings suggest that the implementation of a multicomponent rehabilitation program can improve clinical outcomes in individuals newly diagnosed with idiopathic PD. Our findings underscore the importance of tailored rehabilitation interventions that improve the current standard of care and quality of life for individuals living with PD.

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Poster

PSTR017: Parkinson’s Disease: Clinical Trials

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Topic: C.03. Parkinson’s Disease

Support: American Parkinson’s Disease Association through a Diversity in Parkinson’s Disease Research Grant (APDA/D07)
Parkinson’s Genetics Program (GP2)
ALF is a doctoral student of the Programa de Doctorado en Psicología de la Universidad Nacional Autónoma de México and she is a scholarship holder who received a grant scholarship (1222481) from CONACYT for her Psychology PhD studies

Title: Mental health in Parkinson disease patients in México

Authors: *A. LÁZARO-FIGUEROA[1], A. MORALES DE ARCIA[2], I. HERNÁNDEZ-RUIZ[2], G. DE ANDA MOCTEZUMA[2], P. REYES[3], U. CABALLERO SANCHEZ[2], M. E. RENTERIA[4], S. ALCAUTER[5], A. MEDINA-RIVERA[3], A. E. RUIZ-CONTRERAS[2];
[1]Lab. de Nuerogenómica Cognitiva, Univ. Nacional Autonoma de Mexico, Mexico, City, Mexico; [2]Lab. de Nuerogenómica Cognitiva. Unidad de Investigación en Psicobiología y Neurociencias, Coord. Psicobiología y Neurociencias, Fac. Psicología. Univ. Nacional Autónoma de México (UNAM), Ciudad de México, Mexico; [3]Lab. Internacional de Investigación sobre el Genoma Humano, Univ. Nacional Autónoma de México, Querétaro, Mexico; [4]Queensland Inst. of Med. Res., Herston, Australia; [5]Neurobiología Conductual y Cognitiva, Inst. De Neurobiologia. Univ. Nacional Autónoma de México, Queretaro, Mexico

Abstract: Patients with Parkinson's disease (PD) not only present motor symptoms (e.g. tremor or rigidity) they also experience psychological and psychiatric symptoms. This work aimed to measure and describe the mental health of Mexican patients with PD. The Symptom Checklist (SCL-90r) was used to measure the presence of the discomfort severity symptoms of somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The SCL-90r has an ordinal scale from 0 to 4 for each item; as the score increases, the greater the severity. We compared the severity of distress in each dimension between healthy controls (n=176) and PD patients (n=314) in a subset of data from the Mexican Parkinson's Research Network (MEX-PD). Our results showed that the PD patients have greater severity of symptoms of somatization ($p<0.001$), obsessive-compulsive ($p<0.001$), interpersonal sensitivity ($p<0.001$), depression ($p<0.001$), anxiety ($p<0.001$), phobic anxiety ($p<0.001$), and psychoticism ($p<0.001$) than controls. But hostility ($p=0.047$) and paranoid ideation ($p=0.17$) did not show significant differences (corrected $p<0.006$). These outcomes highlight the increased psychological and psychiatric symptoms in Mexican PD patients respecting controls and matching with those that have been reported in other populations. Because the presence of these symptoms denotes a poor state of mental health, actions must be taken to treat it and improve the patient's quality of life.

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Poster

PSTR017: Parkinson’s Disease: Clinical Trials

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.20/C121

Topic: C.03. Parkinson’s Disease

Title: Evaluation of postural tremor in relation to falls risk in Parkinson's disease

Authors: *N. REILLY[1], J. R. MOXEY[2], P. PRUPETKAEW[2], D. M. RUSSELL[2];
[1]Womack Army Med. Ctr., Fort Liberty, NC; [2]Old Dominion Univ., Norfolk, VA

Abstract: Tremor is a cardinal symptom and one of several motor dysfunctions that can manifest in Parkinson's disease (PD). Numerous factors have been identified as precursors to increases in falls risk in persons with PD such as balance impairments and reductions in strength. However, the relationship between tremor and falls risk in PD has not been thoroughly investigated. This study was conducted to assess differences in tremor characteristics and falls risk between 19 neurologically healthy older adults and 21 older adults with PD. Falls risk was calculated using the Physiological Profile Assessment, a validated battery of assessments of visual contrast, standing balance, lower limb strength, and proprioception where higher composite scores indicate a greater risk of falling. Tremor was assessed using accelerometers (TeleMyo 2400 G2, Noraxon USA, Scottsdale, AZ) affixed to the dorsal aspects of the third metacarpals and tip of the index fingers. Participants were assessed under both a seated and standing posture with their shoulders both flexed at ninety degrees and resting at their sides. Outcome measures for the acceleration signals included amplitudes (root mean square, RMS) and regularity (sample entropy, SampEn) of the collected signals during each condition. Participants with PD displayed significantly greater falls risk scores compared to healthy controls ($p<0.001$). PD participants also exhibited significantly greater RMS of tremor across all testing conditions and bilaterally compared to healthy controls ($p=0.009$). In addition, PD participants displayed reduced regularity of tremor at the hand and finger across multiple conditions compared to healthy controls ($p=0.032$). While both groups displayed significantly greater intra-individual reductions in tremor regularity and increases in amplitudes while standing compared to sitting ($p<0.001$), PD participants exhibited greater intra-individual magnitudes in these changes compared to controls. However, statistically significant correlations between tremor RMS or SampEn and falls risk were limited to being small or weak in nature. Overall, these findings support the notion that posture has a significant pronounced effect on tremor in patients with PD. While these results indicate that posture should be considered when regarding the influence of tremor and motor control, tremor itself, regardless of posture, is not a strong indicator of falls risk within this population.

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Poster

PSTR017: Parkinson's Disease: Clinical Trials

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.21/C122

Topic: C.03. Parkinson's Disease

Support: PMDC Pilot Funding (VCU internal)

Title: Changes in globus pallidus internus local field potentials during freezing-of-gait in Parkinson's disease

Authors: ***J. WALLNER**[1], G. BLACKWELL[2], K. KOLTERMANN[3], G. ZHOU[4], L. CLOUD[2], I. PRETZER-ABOFF[5], K. L. HOLLOWAY[6], D. J. KRUSIENSKI[7];

[1]Virginia Commonwealth Univ., Richmond, VA; [2]Neurol., Virginia Commonwealth Unviersity, Richmond, VA; [3]Col. of William & Mary, Williamsburg, VA; [4]Computer Sci., Col. of William & Mary, Williamsburg, VA; [5]Adult Hlth. and Nursing Systems, Virginia Commonwealth Unviersity, Richmond, VA; [6]Neurosurg., Virginia Commonwealth Univ., Richmond, VA; [7]Biomed. Engin., Virginia Commonwealth Univ., Richmond, VA

Abstract: Freezing-of-gait (FoG) is a common phenomenon in Parkinson's disease and is characterized by the inability to step. This can occur in a variety of scenarios including gait initiation, tight spaces, or distracting environments. FoG's impact on quality of life can range in severity from annoyance to life threatening due to the increased risk of falls it carries. Deep brain stimulation (DBS), an effective and widely used treatment for Parkinson's disease, is currently delivered in a continuous, unchanging manner. The field is pushing toward an adaptable approach where stimulation parameters are adjusted based on changes in the local field potentials they stimulate. If a neural signature associated with FoG could be identified, this could allow for tailored stimulation or external perturbation to shorten the freezing episode or eliminate it all together. Previous studies, which were limited to the subthalamic nucleus, showed that FoG was associated with beta bursts, more prolonged beta just prior to freezing, and excessive synchronization in the 18Hz beta band. This study evaluates the LFPs of the output nucleus of the globus pallidus internus (Gpi) in a real world setting with a sensing-enabled DBS device (Medtronic's Percept), and simultaneous ankle accelerometer data. Five individuals with Parkinson's-related FoG and a Percept DBS system were evaluated on medication and off stimulation. The participants walked an obstacle course of five FoG-triggering scenarios while simultaneous LFPs and ankle accelerometer data were collected. LFPs were analyzed during periods of freezing, standing, and walking. The modulation index, derived from the Kullback-Leibler divergence between the theta phase and various amplitude bands was computed as a measure of phase-amplitude coupling. Preliminary results show that phase-amplitude coupling during freezing followed the trend standing < freezing < walking for the alpha, beta, and gamma amplitude bands. The effect was the most pronounced for theta-gamma coupling. These results suggest that changes in phase-amplitude coupling could be used to identify periods of freezing-of-gait directly from Gpi LFPs.

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Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.01/C123

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: The project that gave rise to these results received the support of a fellowship from "la Caixa" Foundation (ID 100010434). The fellowship code is LCF/BQ/PR23/11980042.

This research was also supported by the Spanish Ministry of Universities via a doctoral fellowship to the first author (FPU21/03459).

Title: Prolonged reduction of tremor over a 2-week period - preliminary results of customized peripheral electrical stimulation in essential tremor patients

Authors: C. MONTERO-PARDO[1], J. PEREZ-SANCHEZ[2], S. SECADES GARCÍA[2], M. PULIDO[1], M. MÚGICA[1], Á. GUTIÉRREZ[3], F. GRANDAS[2], ***F. OLIVEIRA BARROSO**[1]; [1]Neural Engin. Lab, Cajal Institute, Spanish Natl. Res. Council (CSIC), Madrid, Spain; [2]Movement Disorders Unit, Dept. of Neurology, Hosp. Gen. Universitario Gregorio Marañón, Madrid, Spain; [3]E.T.S. Ingenieros de Telecomunicación, Univ. Politécnica de Madrid, Madrid, Spain

Abstract: Essential temblor (ET) is the most common movement disorder, with an estimated prevalence of 5% in the population over 65 years old. Approximately one third of patients with ET are refractory to pharmacological treatments. For those cases, there are alternative options such as deep brain stimulation or ablative surgery (including high-intensity focused ultrasound). However, these interventions are either expensive, invasive or irreversible. Additionally, they may present undesirable adverse effects and not all patients are suitable to undergo these surgical interventions. In the past decade, peripheral electrical stimulation (PES) has been explored as a potential alternative to reduce tremor, avoiding the side effects of drugs and functional neurosurgery. We have previously shown that 10-15 minutes of customized PES below motor threshold reduced considerably tremor in ET patients (in some cases, the effects lasted up to 24 hours), paving the way for a possible therapeutic alternative for those cases refractory to conventional treatments.
To evaluate this application, we delivered PES bilaterally over the nerves innervating wrist flexors and extensors in a group of ET patients. Each patient received daily 20-minute sessions for two consecutive weeks. Clinical scales and kinematics of both arms were assessed daily, before and after each session. Preliminary results show consistent gradual tremor reduction (up to 50%) when comparing tremor power at the wrist joint and the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (FTM) between the first and the last day of treatment.
We are currently evaluating this approach in a higher sample of patients to better understand the capabilities and limitations of a PES-based therapy for tremor management in the long-term. Part of the evaluation includes the assessment of changes in reciprocal inhibition and somatosensory evoked potentials. Our ultimate goal is to develop a setup that can be used daily as a therapy to reduce tremor in the long-term.

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Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

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Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH BRAIN Initiative NINDS Grant UH3NS095553
NSF GRFP

Title: Closed-loop deep brain stimulation for essential tremor: evaluation of speech outcomes

Authors: *A. BURGESS[1], A. GUNDUZ[1], K. FOOTE[2];
[1]Biomed. Engin., [2]Neurosurg., Univ. of Florida, Gainesville, FL

Abstract: Deep Brain Stimulation (DBS) is a known effective therapy for patients with medication-refractory Essential Tremor (ET). Conventional DBS therapy delivers continuous stimulation, which often results in patients experiencing adverse speech artifacts. In ET, dysarthria is a common motor symptom characterized by difficulty forming words or sounds, decreased voice quality, slurring, etc. Closed-loop DBS (CL-DBS) has emerged as an ideal therapy for patients with ET, as stimulation is only delivered when tremor is detected. This can significantly reduce adverse speech-induced artifacts and delivered stimulation continually. Overall, it has been estimated that stimulation-induced speech side effects account for upwards of seventy-five percent of reported ET patients. The objective of this study is to determine speech performance of CL-DBS across various conditions compared to continuous DBS (open-loop DBS; OL-DBS) paradigms with consistent tremor suppression. Five ET patients were implanted unilaterally with the Medtronic RC+S in the ventral intermediate nucleus of the thalamus (VIM). After DBS surgery, patients underwent follow-up for 24 months. This consisted of evaluating motor symptoms of tremor and speech with DBS off, OL-DBS on, and CL-DBS on. Real-time modulation of thalamic recordings of local field potentials (LFPs) were gathered from motor movements in upper limbs, and during speech assessment. Tremor severity was analyzed blindly by a trained neurologist using the Fahn-Tolosa-Marin Tremor Rating Scale (TRS). Speech was assessed through diadochokinesis (DDK) tasks, which involve performing rapid alternating syllable sounds in a controlled period to evaluate dysarthria. The outcome of this study is an exploration of speech performance outcomes of CL-DBS versus OL-DBS in decreasing speech side effects due to tremor suppression of LFPs. CL-DBS personalizes triggering stimulation due to tremor activity, which has shown improvement in speech-motor production. However, there is difficulty in finding a balance between decreasing stimulation-induced speech artifacts while maintaining tremor suppression due to differing optimal DBS parameters. The significance of this work demonstrates immense potential towards improving CL-DBS algorithms, development of future DBS devices, and reducing speech motor symptoms. Additionally, these successes provide the feasibility of creating a simulation condition (CL-DBS) that lessens the involvement of patients in their daily lives (i.e., interchanging groups to mitigate side effects).

Disclosures: **A. Burgess:** None. **A. Gunduz:** 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.; NINDS grant UH3NS095553. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Medtronic provided investigational devices. **K. Foote:** 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.; NINDS grant UH3NS095553.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.03/C125

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: UH3NS095553

Title: Tolerability of closed-loop stimulation of the ventralis intermediate nucleus in essential tremor

Authors: *N. E. GEIGEL[1], J. WONG[2], A. GUNDUZ[3];
[2]Neurol., [3]Biomed. Engin., [1]Univ. of Florida, Gainesville, FL

Abstract: Deep Brain Stimulation (DBS) therapy is an effective treatment for medication refractory essential tremor (ET). The most common brain target for ET DBS is the ventralis intermediate (Vim) nucleus of the thalamus. ET primarily involves an action tremor of the bilateral upper extremities that only occurs during movement. At present, continuous stimulation is the main approach for delivering therapy, but it can lead to unnecessary stimulation during symptom-free periods. A closed-loop DBS system, which activates only during movement-related tremors, could offer a more targeted treatment. Although this method is temporally more accurate and may decrease the likelihood of stimulation-induced side effects, the abrupt onset of stimulation may not be well-received by all patients, which we refer to as "tolerability". In order to responsively stimulate at the onset of movement or tremor to suppress the symptoms, we aimed to increase the slope of the fast ramping rate to reach the therapeutic amplitude faster, while optimizing for tolerability. Here, we report a sub-analysis of a larger prospective clinical trial of closed-loop DBS for ET. We describe our experiences in the programming optimization process of four subjects. We characterize the tolerability of a closed-loop stimulation paradigm across various parameters, including stimulation amplitude, ramp rate, total electrical energy delivered, and their correlations with stimulation-induced paresthesia. One subject (ET01) experienced paresthesia regardless of stimulation ramp rate, and thus did not tolerate closed-loop stimulation. Another subject, ET02, could tolerate the fastest allowable ramp rate when stimulating from contact two on the lead, but when their settings were changed to stimulate from contact one for better tremor control, they could no longer tolerate the state changes at any stimulation ramp rate. The final two subjects (ET03 and ET04) tolerated closed-loop well across various parameter settings. Given these spatial differences, we hypothesize that lead location, relative distances to adjacent neuroanatomy, and patient-specific tissue conductivity may play a role in the tolerance of closed-loop paradigms. These factors may be critically relevant when determining if a candidate is well-suited for closed-loop DBS.

Disclosures: **N.E. Geigel:** None. **J. Wong:** None. **A. Gunduz:** None.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.04/C126

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Parekh Center for Interdisciplinary Neurology
NINDS Grant N131658
Parkinson's Foundation (Columbia University)
P30 AG066462 (Columbia University)

Title: Striatal and cerebellar cell type specific transcriptional dysregulation in multiple system atrophy

Authors: ***T. MA**[1], J.-P. VONSATTEL[2], R. ALCALAY[3], S. A. LIDDELOW[4], U. J. KANG[1]; [1]Neurol. and Neurosci. Inst., NYU Grossman Sch. of Med., New York, NY; [2]Pathology and Cell Biol., Columbia Univ. Med. Ctr., New York, NY; [3]Neurol., Columbia Univ. Med. Ctr., New York, NY; [4]Neurosci. Inst., NYU Grossman Sch. of Med., New York, NY

Abstract: Multiple system atrophy (MSA) is a sporadic progressive neurodegenerative disease clinically defined by autonomic dysfunction with any combination of parkinsonism and cerebellar features. MSA patients are stratified into two main subtypes based on predominant motor phenotype: *MSA-C for cerebellar* and *MSA-P for parkinsonian*, which corresponds to traditional olivopontocerebellar atrophy and striatonigral degeneration, respectively. However, pathology is evident in both brain regions for most patients, indicating common pathogenic processes. Despite widespread neurodegeneration, the pathological hallmark of MSA is the accumulation of fibrillar forms of α-synuclein in glial cytoplasmic inclusions (GCIs) within oligodendrocytes. As overt oligodendrocyte loss is variably reported, the nature of oligodendrocyte dysfunction has been a main focus of MSA pathogenesis research. α-synuclein is expressed at low levels by oligodendrocytes and whether the accumulation of α-synuclein protein within oligodendrocyte is cell autonomous remains debated. Additionally, the factors leading to α-synuclein accumulation (early events) and the subsequent consequences to cellular physiology (late events) remain obscure. We hypothesize that the less affected tissue of each MSA subtype represents earlier stages in the progression of MSA: the striatum for MSA-C and cerebellum for MSA-P. Here we use single nucleus RNA sequencing (snRNAseq) of postmortem striatum (putamen) and cerebellum from MSA-P, MSA-C, and healthy control donors to capture the transcriptional profile of individual cells of nearly all cell types in these tissues to uncover cell type-specific transcriptional alterations and their progression in MSA. We present single cell transcriptomes for 6 control, 5 MSA-P, and 7 MSA-C cases. As with other snRNAseq studies, the transcriptional heterogeneity of recovered cells, including oligodendrocytes, allowed identification of subtypes of each cell class. We found dysregulated

patterns of gene expression common to both MSA-P and MSA-C oligodendrocytes, which formed a cluster that may represent putative pathological cells. The proportion of cells with this "pathological" profile was highest in the striatum for clinically-defined MSA-P and in the cerebellum for MSA-C cases. We are adding additional paired samples of striatal, cerebellar, and cortical tissue to more firmly establish the dysregulated genes that are differentially altered in tissue-selective manners in MSA-P and MSA-C cases and determine their putative contribution to oligodendrocyte dysfunction.

Disclosures: **T. Ma:** None. **J. Vonsattel:** None. **R. Alcalay:** None. **S.A. Liddelow:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstronauTx Ltd., Synapticure. F. Consulting Fees (e.g., advisory boards); Global BioAccess Fund, Tambourine. **U.J. Kang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amprion. F. Consulting Fees (e.g., advisory boards); NurrOn Pharmaceuticals, Inc., UCB Biopharma SRL.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.05/C127

Topic: C.04. Movement Disorders other than Parkinson's Disease

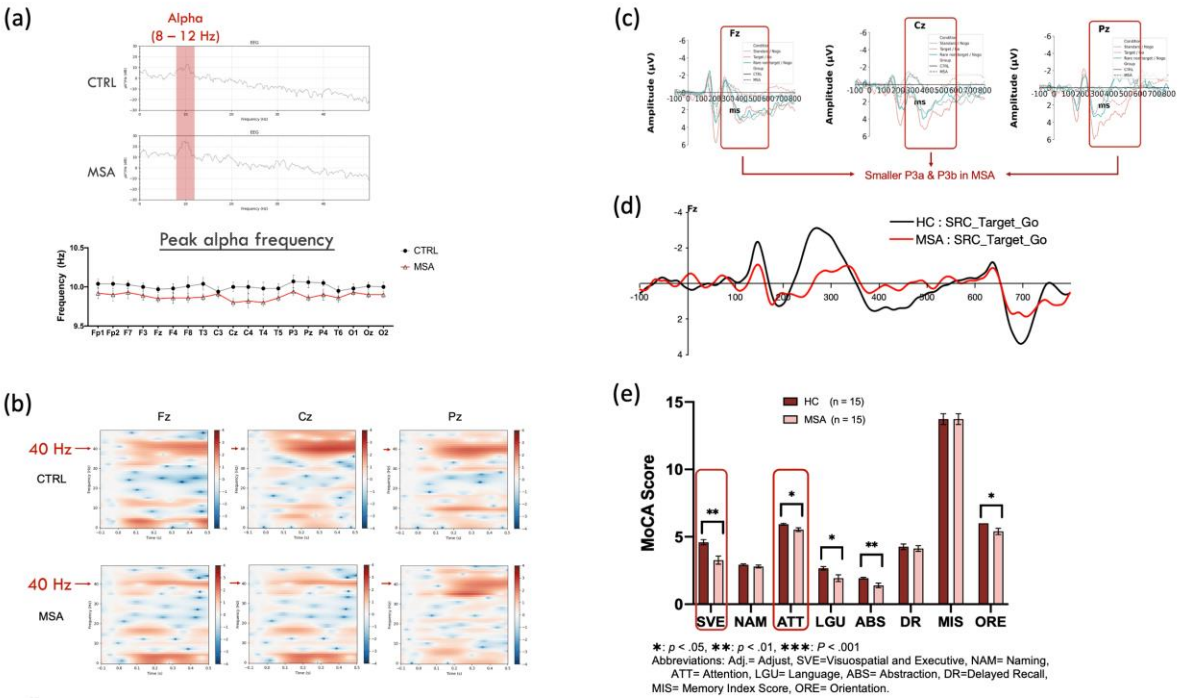
Support: NSTC-112-2321-B-002-022

Title: The lost part of cognitive function in Multiple System Atrophy: alterations in cognitive assessments using EEGs

Authors: ***F.-Y. SU**[1], H.-H. LIU[2], D.-Z. LUO[1], W.-S. LAI[1];
[1]Psychology, Natl. Taiwan Univ., Taipei, Taiwan; [2]Clin. Psychology, Fu Jen Catholic Univ., New Taipei, Taiwan

Abstract: Multiple system atrophy (MSA) is a rare and fatal neurodegenerative disease affecting both motor and cognitive functions in adults. While motor deficits have been extensively studied, understanding cognitive impairments in MSA remains limited. This study aimed to investigate cognitive changes in MSA patients using a comprehensive approach. Fifteen MSA patients and 15 age-sex-matched healthy individuals (mean age: 59 ± 7.03) underwent passive electroencephalogram (EEG) paradigms (resting-state EEG and auditory steady-state response (ASSR)) and active high-level event-related potential (ERP) tests (visual oddball paradigm (VOP) and spatial stimulus-response tasks (SSRT)), along with the Montreal Cognitive Assessment (MoCA). Results revealed reduced cortical excitability and abnormalities in cognitive functions, evidenced by lower peak alpha frequency (PFA) in resting-state EEG (Fig. a) and weaker 40 Hz event-related spectral perturbation (ERSP) during ASSR (Fig. b) in MSA patients. Additionally, MSA patients exhibited diminished amplitudes in attention allocation P3a

and target detection P3b components of VOP (Fig. c), indicating impaired automatic cognitive processing. Heightened efforts in SSRT were observed, reflected in increased N2a components in Fz (Fig. d). MoCA scores showed significantly poorer performance in MSA patients, particularly in visuospatial, executive, and attention domains (Fig. e), potentially aligning with ERP findings. These findings underscore the significant cognitive impairment in MSA patients, emphasizing the necessity for further investigation into high-level cognitive functions to refine clinical diagnosis and management strategies.



Disclosures: **F. Su:** None. **H. Liu:** None. **D. Luo:** None. **W. Lai:** None.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.06/C128

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH/NINDS R01 NS108114

Title: Mechanisms underlying the role of deubiquitinase USP7 in the neurodegenerative CAG triplet repeat disorder spinal and bulbar muscular atrophy

Authors: *M. SENGUPTA[1,2], S. V. TODI[3], D. E. MERRY[4];
[1]Thomas Jefferson Univ., Philadelphia, PA; [2]Department of Biochemistry and Molecular

Biology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA; [3]Dept. of Pharmacol., Dept. of Neurol., Wayne State Univ., Detroit, MI; [4]Dept. of Biochem. and Mol. Biol., Sidney Kimmel Med. Col., Thomas Jefferson Univ., Philadelphia, PA

Abstract: Spinal and bulbar muscular atrophy (SBMA) is a neurodegenerative, neuromuscular disorder affecting males with ≥38 polyglutamine (polyQ)-encoding CAG repeats in the androgen receptor (AR) gene. Upon androgen-binding, expanded polyQ AR (AR^{exp}) misfolds and aggregates, forming nuclear inclusions in affected tissues. Dysfunction and cell loss within the neuromuscular system manifests as muscle atrophy, impaired mobility, dysphagia, and dysarthria. We previously showed that deubiquitinase USP7 alters AR^{exp} ubiquitination at 8 lysines (8K), and that USP7 knockdown ameliorates AR^{exp} aggregation and associated cell toxicity. Mutating one of these sites to arginine (K17R) to block ubiquitination increased AR^{exp} aggregation, suggesting that deubiquitination at K17 plays an important role in SBMA pathogenesis. The current study focuses on determining whether USP7 promotes AR^{exp} aggregation primarily via its actions on K17, on all 8K, or on (an)other protein(s) besides AR^{exp}. We created stable PC12 cell lines expressing doxycycline-inducible AR^{exp} with KR mutations to prevent ubiquitination at either K17 (AR^{exp} K17R) or at all 8K sites (AR^{exp} 8KR). Additionally, we created doxycycline-inducible AR^{exp} K17R cell lines with stable USP7 knock-down. We found that USP7 knockdown in AR^{exp} K17R cells does not decrease AR^{exp} aggregation, suggesting that K17 is an important site of USP7-mediated deubiquitination through which it contributes to AR^{exp} aggregation. We are currently evaluating a proteolysis-targeting chimera (PROTAC) degrader of USP7 in order to test if pharmaceutical USP7 reduction recapitulates the effect of genetic USP7 reduction in these cells. Unexpectedly, we found that AR^{exp} 8KR cells have less AR^{exp} aggregation relative to AR^{exp} K17R cells, suggesting that ubiquitination on either all 8 lysines, or on one (or more) of the other 7 lysines promotes AR^{exp} aggregation. Our ongoing studies continue to investigate the molecular mechanisms underlying the role of ubiquitination and USP7-mediated deubiquitination in AR^{exp} degradation and aggregation in SBMA pathogenesis. We expect that results from the above studies will elucidate the mechanistic role of USP7 and AR^{exp} ubiquitination/deubiquitination in SBMA.

Disclosures: **M. Sengupta:** None. **S.V. Todi:** None. **D.E. Merry:** None.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.07/C129

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: National Science Foundation 2244127
University of Delaware Research Foundation
Delaware Bioscience Center for Advanced Technology
American Academy for Cerebral Palsy and Developmental Medicine

Pedal with Pete Foundation award
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Title: Regulation of transcription factor MEF2C expression by circNFIX in spastic cerebral palsy

Authors: *B. ROMERO CARPIO[1], P. HOQUE[1], K. ROBINSON[2], S. K. YEAGER[2], V. PARASHAR[1], R. E. AKINS[2], M. BATISH[1];
[1]Med. and Mol. Sci., Univ. of Delaware, Newark, DE; [2]Nemours Children's Hlth. Syst., Wilmington, DE

Abstract: Spastic cerebral palsy (CP) accounts for more than 80% of CP cases and involves conditions such as muscle hypertonia, contracture, and musculoskeletal deformities that often worsen over time. Unpublished data from our group has found that the expression of circular RNA (circRNA), circNFIX is altered in muscle cells from CP patients. CircRNAs are regulatory RNAs that play crucial roles in modulating gene expression through their ability to “sponge” regulatory microRNAs (miRNAs). Here, we used primary myoblasts (MBs), and myotubes (MTs) to explore the role of circNFIX in regulating the expression of MEF2C, a transcription factor that plays a critical role in muscle development and sarcomere formation. Under an IRB-approved protocol, MBs were obtained from surgical samples of skeletal muscle and subsequently differentiated into MTs. Isolated cells from study participants with CP (n=9) and non-CP controls (CN) (n=9) were validated by immunostaining for PAX7 and MYF5. qRT-PCR analysis was performed to estimate the level of circNFIX and MEF2C in MBs, MTs, and skeletal muscle tissue. Additionally, MEF2C protein expression was assessed in MBs and MTs by immunofluorescence. Moreover, the expression of downstream targets of MEF2C was evaluated by qRT-PCR. Bioinformatic analyses were performed to identify miRNAs targeting MEF2C and regulated by circNFIX. The relationship of the circRNA/miRNA/mRNA axis on MEF2C was evaluated by dual-luciferase assay using a mimic of the target miRNA and a negative control miRNA.We observed reduced circNFIX and MEF2C levels in CP MBs, MTs, skeletal muscle tissue compared to controls. The protein level of MEF2C was significantly decreased in both CP and KD MB cells, leading to a reduction in the level of downstream MEF2C targets, including Myomesin 1 and 3, and Myozenin 2. Bioinformatic analysis identified miR373-3p as a potential target of circNFIX. Regulation of MEF2C levels by miR373-3p was impacted by circNFIX levels in cells from CP and CN samples. These findings support our hypothesis that circNFIX downregulates the translation of MEF2C protein by sponging of miR-373-3p. The regulatory circNFIX/MEF2C/miRNA373-3p axis could help explain the development of shortened and overstretched sarcomeres in CP. Being highly expressed and having a functional role, circNFIX could be explored as a potential non-invasive diagnostic biomarker as well as a potential therapeutic target for CP.

Disclosures: B. Romero Carpio: None. **P. Hoque:** None. **K. Robinson:** None. **S.K. Yeager:** None. **V. Parashar:** None. **R.E. Akins:** None. **M. Batish:** None.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.08/C130

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Unraveling the inflammatory landscape in X-linked dystonia parkinsonism

Authors: *R. MONSANTO[1], M. MURPHY[2], T. PETROZZIELLO[3], M. G. MURCAR[4], E. PENNEY[2], R. F. SÎRBULESCU[5], P. REEVES[6], G. SADRI-VAKILI[7];
[1]Mass Gen. Brigham, Boston, MA; [2]Massachusetts Gen. Hosp., Boston, MA; [3]Neurol., Mass Gen. Brigham, Boston, MA; [4]Neurol., Massachusetts Gen. Hosp., Boston, MA; [5]Neurol., Harvard Med. Sch., Boston, MA; [6]Surgery, MGH, Boston, MA; [7]Dept Neurol., Massachusetts Gen. Hosp., Charlestown, MA

Abstract: We have recently demonstrated that neuroinflammation, a process widely described in neurodegenerative diseases, could also play a role in the pathogenesis of X-linked Dystonia Parkinsonism (XDP). Our previous findings demonstrated a significant increase in astrogliosis and microgliosis in human post-mortem prefrontal cortex (PFC) derived from people who lived with XDP. We also found an increase in myeloperoxidase (MPO) levels and activity in XDP PFC, suggesting that peripheral immune cells may infiltrate the central nervous system (CNS) in XDP given that MPO is mainly released by neutrophils and macrophages. Interestingly, glial cells - reactive astrocytes and activated microglia - have also been shown to release MPO. Therefore, we sought to determine the source of MPO - peripheral vs innate immune cells - in XDP by characterizing the molecular inflammatory landscape in post-mortem brain samples. We used imaging mass cytometry, a novel imaging approach that allows the assessment of up to forty different antibodies in a single experiment. Specifically, we tested 30 antibodies in human post-mortem PFC and identified a panel of 10 antibodies - GFAP, CD68, MMP9, CD3, CD45, CD163, CD4, CD8, neutrophil elastase, and Ki67, that were used for our IMC study. Protein levels and localization were measured in XDP, cerebrovascular disease (CVD), and Huntington's disease (HD), as well as non-neurological control PFC post-mortem samples. Our results revealed no change in the levels of the 9 proteins from our panel between XDP, CVD, or HD compared to controls. However, there was a significant decrease in MMP9 levels in XDP PFC compared to non-neurological controls. We correlated protein levels with XDP clinicopathological features, including age at disease onset, age at death, and disease duration. Although there was no significant change in protein levels, there was a significant impact of GFAP and neutrophil levels on age at disease onset, and age at death, suggesting that higher levels of GFAP and neutrophils may be involved with XDP disease progression. Taken together, our results confirm our previous findings that increases in astrogliosis may be involved in XDP pathogenesis, and highlight neutrophils as another cell type that may worsen disease progression.

Disclosures: R. Monsanto: None. **M. Murphy:** None. **T. Petrozziello:** None. **M.G. Murcar:** None. **E. Penney:** None. **R.F. Sîrbulescu:** None. **P. Reeves:** None. **G. Sadri-Vakili:** None.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.09/C131

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Collaborative Center for X-Linked Dystonia-Parkinsonism
Leon Levy Fellowship in Neuroscience
The National Human Genome Research Institute Centers of Excellence in Genomic Science program
MD Anderson Neurodegeneration Consortium

Title: What are the cellular and molecular drivers of striatal neurodegeneration?

Authors: *P. PRAKASH[1], W. ZHANG[2], Y. ZHAO[2], K. C. LIMBERG[3], B. C. VILNAIGRE[3], C. F. LABORC[4], A. O'KEEFFE[3], H. APPLEBY[5], A. C. MAR[6], R. BROSH[2], J. BOEKE[2], S. A. LIDDELOW[4];
[1]NYU Grossman Sch. of Med., New York, NY; [2]Inst. for Systems Genet., NYU Langone Hlth., New York, NY; [3]NYU Sch. of Med., New York, NY; [4]Neurosci. Inst., NYU Sch. of Med., New York, NY; [5]Inst. for Systems Genet., New York, NY; [6]Neurosci. and Physiol., Neurosci. Inst., NYU Sch. of Med., New York, NY

Abstract: X-linked Dystonia Parkinsonism (XDP) is a rare, X-linked recessive neurodegenerative movement disorder characterized by the preferential loss of striatal medium spiny neurons (MSNs). XDP is caused by a disease-specific SINE-VNTR-Alu (SVA) retrotransposon insertion in the ubiquitous *TAF1* gene, which encodes the TATA-binding protein associated factor 1, known for its indispensable role in transcription and cell viability. Two factors have limited our understanding of XDP pathology. First, since TAF1 is expressed in all cells, the contribution of individual cell types to the disease is not defined. Second, since SVAs are found solely in primates (including humans), we have not been able to replicate disease phenotypes using a relevant *in vivo*rodent model. To address these challenges, we have engineered a humanized model of XDP ($TAF1^{PC\text{-}XDP}$), which has a conditional hybrid mouse/human version of the *TAF1* locus. This engineered locus contains exons 1-24 of mouse (m) *Taf1* and exons 25-38 of the human (h) *TAF1* gene. A single XDP-causing SVA insertion is included in the intron 32 of the human *TAF1* region. When crossed with cell-type specific Cre-expressing mice, these unique XDP model mice replace exons 25-38 of m*Taf1* and replace it with the corresponding SVA-containing h*TAF1* region. This unique mouse can be used to study the contribution of individual cell types to XDP phenotype. To determine the contribution of neural cells to XDP, we established a $Nestin^{Cre}Taf1^{XDP}$ mouse line in which the disease specific SVA insertion *Taf1* is specifically driven by $Nestin^{+}$ cells. Compared to the Cre control mice, the resulting $Nestin^{Cre}Taf1^{XDP}$ males have significantly reduced body weight, and none survive beyond ~60 days. Strikingly, the $Nestin^{Cre}Taf1^{XDP}$ males have drastically reduced brain size, enlarged lateral ventricles, and a profound striatal atrophy. Female $Nestin^{Cre}Taf1^{XDP}$ mice appear to be grossly normal. We next assessed the motor function of these XDP animals. The $Nestin^{Cre}Taf1^{XDP}$males exhibited abnormal gait and reduced motor performance, similar to human patients. Finally, we asked what are the molecular underpinnings that may describe these severe symptoms. Immunohistochemistry revealed increased presence of apoptotic markers in the striatum but not cortex of the XDP animals. We also observed an increase in inflammatory

markers in the striatum, including neurotoxic reactive astrocytes ($C3^+GFAP^+$ cells) and microglia ($CD68^+IBA1^+$ cells), respectively. Ongoing molecular analysis of these brain regions aims to identify the cell-specific molecular drivers of XPD and explore potential treatment pathways for this rare disease.

Disclosures: P. Prakash: None. **W. Zhang:** None. **Y. Zhao:** None. **K.C. Limberg:** None. **B.C. Vilnaigre:** None. **C.F. Laborc:** None. **A. O'Keeffe:** None. **H. Appleby:** None. **A.C. Mar:** None. **R. Brosh:** None. **J. Boeke:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neochromosome, Inc.. F. Consulting Fees (e.g., advisory boards); ReOpen Diagnostics, LLC, Sangamo, Inc, Modern Meadow, Inc, Rome Therapeutics, Inc, Sample6, Inc, Tessera Therapeutics, Inc, Wyss Institute. **S.A. Liddelow:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstronauTx Ltd.. F. Consulting Fees (e.g., advisory boards); BioAccess Fund, Tambourine, Synapticure.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.10/C132

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: 5UH3NS119844
G130253

Title: Advancements in Closed-Loop Deep Brain Stimulation for Tourette Syndrome: A Multi-Nuclei Approach

Authors: *J. GOMEZ[1], G. LOWOR[1], M. S. OKUN[1], K. FOOTE[1], A. GUNDUZ[2];
[1]Univ. of Florida, Gainesville, FL; [2]Biomed. Engin., Univ. of Florida, Gainesville, FL

Abstract: Tourette Syndrome (TS) poses significant challenges in management, with Deep Brain Stimulation (DBS) emerging as a promising therapeutic avenue. This study explores the efficacy of closed-loop DBS targeting the centromedian (CM) nucleus and anterior globus pallidus interna (aGPi) in alleviating TS symptoms. Over nine months, our research undergoes several phases, including the identification of optimal nuclei for tic detection and suppression, fine-tuning adaptive settings, and testing these parameters. Data collection involves diverse conditions, including rest periods and natural tic expression, recorded with Medtronic Percept implants and Delsys sensors. Initial findings from our four-subject cohort, predominantly female, with bilateral macroelectrodes implanted in the CM and aGPi, alongside bilateral Percept neurostimulators, reveal consistent separability of tics from rest in lower frequency bands (1-10 Hz). Despite hardware limitations, closed-loop DBS utilizing the LFP signal is successfully initiated. However, ongoing analysis indicates notable divergence in optimal sensing and stimulation target pairings among subjects. For instance, while some subjects benefit from CM

stimulation, others show optimal outcomes with aGPi stimulation, highlighting the importance of individualized therapy. Moving forward, our trajectory involves not only refining DBS parameters but also investigating the impact of CM and aGPi stimulation on TS-associated psychiatric comorbidities. Given the observed variations in optimal sensing and stimulation pairings, individual differences, including psychiatric comorbidities, may influence treatment efficacy. Regular assessment of stimulation thresholds is crucial to sustain therapeutic benefits and prevent habituation. Additionally, efforts to streamline tic detection during patient visits are underway, recognizing the time-intensive nature of current video labeling techniques. Our overarching aim is to optimize closed-loop DBS targeting CM or aGPi for TS treatment, thereby enhancing treatment outcomes and improving the quality of life for individuals with TS.

Disclosures: J. Gomez: None. **G. Lowor:** None. **M.S. Okun:** None. **K. Foote:** None. **A. Gunduz:** None.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.11/Web Only

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Avery project

Title: A HEREDITARY SPASTIC PARAPLEGIA DUE TO MUTATIONS IN SPTSSA MAY BE MODIFIED BY INHIBITION OF SERINE PALMITOYLTRANSFERASE

Authors: *Y. GONG[1], A. GLOVER[2], K. GABLE[3], T. DUNN[3], F. EICHLER[1]; [2]Neurol., [1]Massachusetts Gen. Hosp., Boston, MA; [3]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Sphingolipids are a diverse family of lipids with critical structural and signaling functions in the mammalian nervous system. Serine palmitoyltransferase (SPT) catalyzes the rate-limiting reaction of sphingolipid synthesis and is comprised of multiple subunits including an activating small subunit, SPTSSA. Sphingolipids are both essential and cytotoxic and their synthesis must therefore be tightly regulated. Exome sequencing identified potentially disease-causing variants in SPTSSA in three children presenting with a complex form of hereditary spastic paraplegia. The effect of these variants on the catalytic activity and homeostatic regulation of SPT was investigated in human embryonic kidney cells and patient fibroblasts. A new mouse model harboring the SPTSSA T51I mutation that was created and characterized. Therapeutic options in this model were explored based on the presumed pathogenesis. Our results showed that two different pathogenic variants in SPTSSA caused a hereditary spastic paraplegia resulting in progressive motor disturbance with variable sensorineural hearing loss and language/cognitive dysfunction in three individuals. The variants in SPTSSA impaired the negative regulation of SPT by ORMDLs leading to excessive sphingolipid synthesis based on

biochemical studies. Mice harboring the SPTSSA T51I mutation displayed increased sphingolipid (SL) accumulation and a neurological phenotype, both exacerbated by serine supplementation. Treatment with the SPT inhibitor myriocin significantly reduced SL accumulation and rescued the phenotype.

Disclosures: Y. Gong: None. **A. Glover:** None. **K. Gable:** None. **T. Dunn:** None. **F. Eichler:** None.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.12/C133

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: F.No. 45/16/2022-PHA/BMS

Title: Activation of G- Protein-Coupled Estrogen Receptor (GPER) ameliorates haloperidol-induced neurotoxicity in shsy5y cells and adult zebrafish through activation of genomic signaling pathway

Authors: *S. UPADHAYAY[1], P. KUMAR[2];
[1]Pharmacology. Div. Neurobio., Central Univ. of Punjab, Bathinda, India; [2]Pharmacol., Central Univ. of Punjab, Bhatinda, India

Abstract: Background: Tardive dyskinesia (TD) is a severe neurological condition, that occurs after long-term use of typical antipsychotic drugs, characterized by irregular involuntary movements, targeting the orofacial region. The raloxifene and fulvestrant have similar pharmacological properties as identified in 17β estradiol a well-known estrogen receptor modulator and G-Protein-Coupled Estrogen Receptor 30 (GPR30) activator showing anti-oxidant, anti-inflammatory, and antiapoptotic properties against neurological disorders. **Aim:** The study aimed to investigate the effect of raloxifene and fulvestrant against haloperidol-induced neurotoxicity in SHSY-5Y cells and adult zebrafish. **Methods:** In this study, SHSY-5Y cell lines were treated with raloxifene (0.01µM), and fulvestrant (d 0.01µM) 1 hour before haloperidol (100 µM). The study used GPR30 antagonist G-15 (1µM) and agonist G-1 (2 µM). Furthermore, a total of 48 adult zebrafish were divided into 4 groups (n 12), Apoptosis was examined by using a confocal microscope, RT-PCR was utilized to estimate the RNA expression and western blot was used to estimate GPR30 expression in the groups. **Results:** Haloperidol treatment reduced 50% cell viability than the control groups, whereas, pretreatment of raloxifene and fulvestrant significantly increased the cell viability of haloperidol-treated group. Moreover, G1 agonists increase cell viability the haloperidol-treated group. In addition, raloxifene and fulvestrant reduced ROS generation and apoptosis cell death in haloperidol treated group. While, raloxifene and fulvestrant enhanced the RT-PCR expression of Nrf2 and HO-1 levels in SHSY-5Y cells as well as western blot expression of GPR30 as compared to the haloperidol-treated

group. In an in-vivo study, raloxifene (10 ug/kg) and fulvestrant (10 ug/kg) enhance the total distance travelled, mean speed, and decrease in catalepsy behaviour in an adult zebrafish as compared to alone haloperidol-treated group. Similarly, raloxifene (10 ug/kg) and fulvestrant (10 ug/kg) significantly decreased the number of entries in the bottom zone and increased entries in the top zone in the novel diving tank as compared to haloperidol-treated group. Additionally, treatment with raloxifene and fulvestrant significantly increased antioxidants in zebrafish brains as compared to the toxin group. **Conclusion:** Findings suggest that raloxifene and fulvestrant can activates GPR30 expression and upregulates the Nrf2 and HO 1 signaling pathways showing a neuroprotective effect against haloperidol-mediated toxicity.

Disclosures: S. Upadhayay: None. **P. Kumar:** None.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.13/C134

Topic: C.06. Neuromuscular Diseases

Support: Luminesce Alliance
National Health and Medical Research Council (APP2002640, APP1121651)
Medical Research Future Fund, Rapid Applied Research Translation Program grant awarded to Sydney Health Partners

Title: Genetic variants in CDK5RAP3 in two siblings with neonatal-lethal fetal akinesia and pontocerebellar hypoplasia

Authors: *M. YUEN[1,2,3,4], R. G. MARCHANT[5,2,4], K. ZHANG[5,2,4], R. ISHIMURA[6], M. E. GRAHAM[7], M. T. AUNG-HTUT[8], H. JOSHI[9,10,2], R. J. LEVENTER[11], M. KOMATSU[12], F. J. EVESSON[13,4,10], S. T. COOPER[14,10,2];
[1]Children's Med. Res. Inst., Westmead, Australia; [2]SoMS, University of Sydney, Sydney, Australia; [3]University of New South Wales, Randwick, Australia; [4]Kids Neuroscience Centre, Kids Research, The Children's Hospital at Westmead, Westmead, Australia; [5]Functional Neuromics, Children's Med. Res. Inst., Westmead, Australia; [6]Dept. of Physiol., Juntendo Univ. Sch. of Med., Tokyo, Japan; [7]Biomed. Proteomics, Children's Med. Res. Inst., Westmead, Australia; [8]Ctr. for Mol. Med. and Innovative Therapeut., Murdoch Univ., Murdoch, Australia; [9]Kids Neurosci. Ctr., Kids Res., The Children's Hosp. at Westmead, Westmead, Australia; [10]Functional Neuromics, Children's Medical Research Institute, Westmead, Australia; [11]Royal Children's Hosp. Melbourne, Melbourne, Australia; [12]Dept. of Physiol., Juntendo Univ. Sch. of Med., Bunkyo-ku, Japan; [13]SoMS, Univ. of Sydney, Sydney, Australia; [14]Kids Neurosci. Ctr., Kids Res., The Children's Hosp. at Westmead, Westmead, Australia

Abstract: A genetic diagnosis for individuals with inherited neurological disorders is critical to ensure optimal clinical care for affected families, including access to available therapies and genetic counselling/family planning. Despite significant improvements in the diagnosis of rare genetic disorders, variants in some parts of the genome remain difficult to interpret - requiring advanced analyses such as RNA sequencing and functional laboratory studies.
Here we describe two siblings with neonatal-lethal fetal akinesia, global growth restriction, liver fibrosis, pontocerebellar hypoplasia and histological abnormalities (including simplified olives and reduced Purkinje cell number). Using whole genome and RNA sequencing we discovered a segregating, homozygous deep-intronic variant in a novel disease gene, *CDK5RAP3* (NM_176096.3 c.409+243G>A). To confirm pathogenicity of the genetic variant and characterise *CDK5RAP3*-related disease in probands, we performed mRNA and protein expression analyses.
We established that the deep-intronic variant induces abnormal pre-mRNA splicing, resulting in the inclusion of a pseudoexon into canonical *CDK5RAP3* transcripts. The pseudoexon encodes a premature termination codon, causing nonsense-mediated decay of transcripts and markedly reduced levels of full-length CDK5RAP3 protein. A small amount of canonically spliced *CDK5RAP3* is detected (<2% of control levels). Consistent with the known critical role of CDK5RAP3 in protein UFMylation, patient cells show reduced di-ufmylation of RPL26 and increased UFBP1 ufmylation. An antisense oligonucleotide (ASO), developed to block the inclusion of the pathogenic pseudoexon into mRNA, restores canonical splicing and CDK5RAP3 protein expression. Preliminary proteomic studies show that ASO-mediated restoration of CDK5RAP3 protein expression was able to restore normal expression of several proteins, suggesting these proteins are likely critically dependent on CDK5RAP3.
In conclusion, we have compelling evidence supporting biallelic variants in *CDK5RAP3* as a novel cause of neonatally-lethal fetal akinesia and recommend screening of *CDKRAP3* in undiagnosed individuals presenting with pontocerebellar hypoplasia. Molecular defects of UFMylation detected may suggest pathology relates to abnormal endoplasmic reticulum ribosome- associated protein quality control and ongoing proteomics analysis will shed further light on the molecular mechanism of pathology due to CDK5RAP3 loss. Our study highlights that CDK5RAP3 protein plays a vital role in human neurodevelopment.

Disclosures: **M. Yuen:** None. **R.G. Marchant:** None. **K. Zhang:** None. **R. Ishimura:** None. **M.E. Graham:** None. **M.T. Aung-Htut:** None. **H. Joshi:** None. **R.J. Leventer:** None. **M. Komatsu:** None. **F.J. Evesson:** None. **S.T. Cooper:** None.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.14/C135

Topic: C.04. Movement Disorders other than Parkinson's Disease

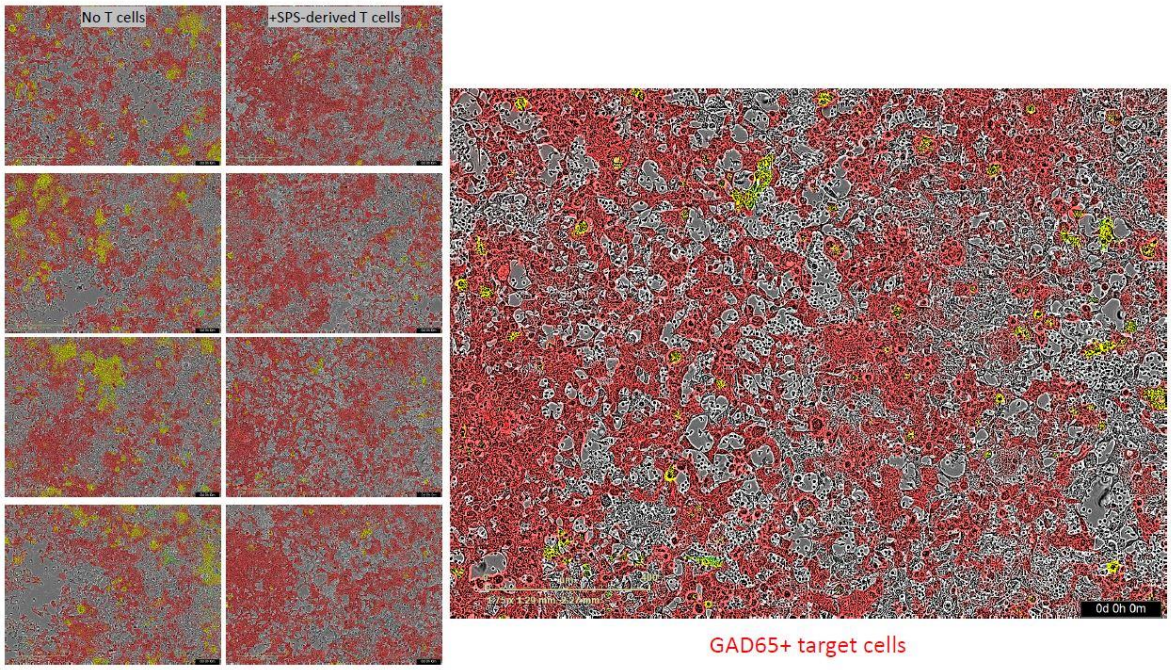
Support: Aditxt Immune Health(2023-504798-19-00)

Title: Characterize GAD65-specific T cell Responses in Patients with Stiff-Person Syndrome and Type-I Diabetes

Authors: *P. SHANG[1], C. HOWE[2], B. CLARKSON[3];
[1]Mayo Clin., Rochetser, MN; [2]Neurol., Mayo Clin., Rochester, MN; [3]Mayo Clin., Rochester, MN

Abstract: Background: Glutamic acid decarboxylase 65 (GAD65) antibodies of any titer can be found in patients with Type I diabetes mellitus (DM1) while high-titer GAD65 antibodies can be detected in CSF and serum from patients with neurological autoimmunity presenting as stiff-person syndrome (SPS). However, given its intracellular localization a direct pathogenic role for GAD65 autoantibodies is not expected and these antibodies likely serve as a surrogate marker for cell-mediated autoimmunity. Namely, it is unproven that CD8+ T cells recognizing GAD65 peptides are directly cytotoxic to GAD65+ inhibitory neurons.
Design/Methods: We utilized full-length GAD67, GAD65 proteins, and 226 overlapping 15-mer peptides covering full sequence of the two proteins to treat autologous PBMC-derived dendritic cells (DCs) from patients with SPS (n=5), DM1 (n=4) and healthy controls (n=12). We further co-cultured autologous T cells with DCs and measured the T cell activation via cytometric bead array, FluoroSpot, and Flow Cytometry. Direct cytotoxicity was measured by coculturing patient CD8+T cells with GAD65+ target cells via live cell imaging.
Results: Using the peptidome methodology, we identified the same 5/46 built peptide pools that elicited T cell activation by multiple metrics and measured the capacity of individual peptides within these pools to activate patient T cells in both DM1 and SPS. We found 10-30% increase in the CD8+CD69+ T cell subpopulations and 5-time elevation of CD8+IL-2+ T cells after irritation from peptides of interest. Predicted affinity for patient HLA class I allotypes was analyzed by NetMHCpan4.1. Lastly, we report the capacity of patient CD8+ T cells to induce direct cytotoxicity and eliminate target cells within 48 hours ($p < 0.01$, Student's T test).
Conclusions: We identified and demonstrated that specific GAD65 peptides can activate cytotoxic T cells in patients with SPS and DM1.We provide valid evidence for cytotoxic T cell pathogenic roles and potential peptide sequence for counteracting the combination between T cell receptors and MHC-I presented antigens in SPS.

CD8+ T cells from Patient with Stiff-Person Syndrome Cause Direct Cytotoxicity to GAD65+ Target Cells



Disclosures: **P. Shang:** None. **C. Howe:** None. **B. Clarkson:** None.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.15/C136

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: US-Israel Binational Science Foundation Award (2019270)
Israel Science Foundation (grant number 1706/22)

Title: Mutation in Protein Kinase A R1 beta (PRKAR1B) gene drives pathological mechanisms of neurodegeneration across species

Authors: *R. ILOUZ[1], A. DAKWAR[2];
[1]Bar Ilan Univ., Safed, Israel; [2]Fac. of Med., Bar Ilan Univ., Safed, Israel

Abstract: Protein Kinase A (PKA) neuronal function is controlled by the interaction of a regulatory (R) subunit dimer to two catalytic (C) subunits. Recently, the L50R variant in the gene encoding to the RIβ subunit was identified in individuals with a novel neurodegenerative disease. However, the mechanisms driving the disease phenotype remained unknown. We reveal that RIβ is an aggregation-prone protein that progressively accumulates in wildtype and Alzheimer's mouse models with age, while aggregation is accelerated in the RIβ-L50R mouse

model. We define RIβ-L50R as a causal mutation driving an age-dependent behavioral and disease phenotype in human and mouse models. Mechanistically, this mutation disrupts RIβ dimerization, leading to aggregation of its monomers. Intriguingly, interaction with the C-subunit protects the RIβ-L50R from self-aggregating, in a dose-dependent manner. Furthermore, cAMP signaling induces RIβ-L50R aggregation. This study sheds light on a remarkably under-appreciated common mechanism across neurodegenerative diseases driven by mutations at dimer interface.

Disclosures: R. Ilouz: None. **A. Dakwar:** None.

Poster

PSTR018: Cellular and Molecular Mechanisms of Other Movement Disorders

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.16/C137

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

Support: NIH

Title: Prenatal Exposure to Beta-methyl-amino-L-alanine (BMAA) Unveil a Novel Model of Amyotrophic Lateral Sclerosis-Parkinson's Dementia Complex in Mice

Authors: *G. MUTHIAN[1], P. PRAKASH[1], R. CHAKRABORTY[1], C. DASH[1,2], C. G. CHARLTON[1];
[1]Biochemistry, Cancer Biol., Neurosci. and Pharmacol., Meharry Med. Col., Nashville, TN;
[2]Department of Microbiology, Immunology and Physiology, Meharry Medical College, Nashville, TN

Abstract: Amyotrophic Lateral Sclerosis-Parkinson's Dementia Complex (ALS-PDC) is a severe neurological disorder, caused by degeneration of upper motor glutamine (UMG), nigrostriatal dopamine (NSDA) and basal forebrain acetylcholine (BFbA) neurons, and locally called Lytico-bodig in Guam. The incidence of ALS-PDC has decline, but the cause is still unknown. Several studies indicate that beta-methylamino-L-alanine (BMAA), a non-protein amino acid, consumed in food prepared from the cycad plant, is the cause of ALS-PDC. The consumption of BMAA has been reduced, as well as the incidence of ALS-PDC, and these implicate BMAA as a likely cause for ALS-PDC, Studies, however, had produced no good model of ALS-PDC. Since UMG, NSDA and MFbA neurons are impaired in ALS-PDC, we targeted these neuronal groups in the fetus, by exposing C57BL/6J pregnant mice to BMAA during gestation day 8-18, the birth or neurogenesis of these neurons in the fetus. The goal was to produce impaired neurons that will succumb/die early during aging. The outcomes showed post-natal changes in weight, behaviors, muscle functions as well as other neurochemicals. Western blot analysis showed that Prenatal BMAA reduced the tyrosine hydroxylase in cortex and midbrain in dose dependent manner. α- synuclein was increased in dose dependent manner in midbrain, forebrain cortex, however it was decreased in the striatum. The neuro filament-L

was significantly increased in midbrain, cortex and. However, it was decreased in hindbrain and hippocampus. The Neurofilament-M was significantly reduced in dose dependent manner in the cortex. However, Neurofilament-H was significantly increased in striatum of all groups when compared to control. The Tau was significantly increase in striatum, cortex and hindbrain however it was markedly decreased in midbrain. TDP43 was increase in hindbrain in prenatal BMAA exposed groups when compared to prenatal PBS. The reduced locomotor and the marker protein changes showed new model for ALSPDC and the outcome suggests that some cases of idiopathic ALSPDC may have a fetal basis in which early subtle nigrostriatal, cholinergic neurons impairments occurred and ALSPDC symptoms are precipitated later by deteriorating changes in the nigrostriatum and cholinergic neurons that caused symptoms in individuals with normal neuronal system.

Disclosures: G. Muthian: None. **P. Prakash:** None. **R. Chakraborty:** None. **C. Dash:** None. **C.G. Charlton:** None.

Poster

PSTR019: Neuroinflammation: Microglia

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.01/C138

Topic: B.09. Glial Mechanisms

Support: Lafayette Parish Medical Society Endowed Professorship
UL Lafayette, GSO
McNair Scholars Program
University of Louisiana at Lafayette Undergraduate Mini Grant

Title: Analysis of pro-inflammatory cytokine gene expression and microglia population in mouse brain following maternal separation

Authors: *T. SUPTY[1], T. L. CAIN[1], A. DOBARD[2], K. M. SMITH[3];
[1]Univ. of Louisiana at Lafayette, Lafayette, LA; [2]Univ. of Louisiana at Lafayette, New Orleans, LA; [3]Dept. of Biol., Univ. of Louisiana at Lafayette, Lafayette, LA

Abstract: Early life experience is an important factor that molds children's neural and psychological development. Infancy and early childhood are periods of particularly high rates of synaptic growth and are therefore the most crucial stage during which environment experiences can have long-lasting effects upon a wide range of developmental domains. Adverse Childhood Events (ACE) encompass any social, familial, and individual forms of stress or mistreatment experienced before the age of 18. Sixty percent of adults from multiple countries report having at least one ACE, with 1 out of 6 people having more than four ACEs. A significant dose-response relationship between ACE count and increased risk of health problems, developmental difficulties, and neuropsychiatric disorders have been found including Mood Disorders, Post-Traumatic-Stress-Disorder (PTSD), Substance abuse disorders, Schizophrenia etc. We utilize a

maternal separation paradigm to simulate early life stress in mice, a widely used rodent experimental model that affects the development of the Hypothalamic-Pituitary-Adrenal (HPA) axis and the methylation status of the glucocorticoid receptor (GR) promoter, crucial factors in emotional processing and anxiety-related behaviors. It entails separation of pups from their mother for 3 hours every day from P1 to P14. We used tgFGFR1-eGFP and Swiss-Webster mice of both sexes for this project. Through qPCR and immunohistochemistry, a significant upregulation of Interleukin-6 (*IL-6*) gene expression in the entire brain and Fibroblast Growth Factor Receptor (*Fgfr1*) within the anterior cingulate cortex was observed. An increase in neuronal populations identified by neuronal nuclei (NeuN) was also found. Neuroinflammation, assessed by studying microglia number and activation status, expression of Interleukin-1β, and complement protein C1q following maternal separation is also being assessed. Imbalances in active-state and resting-state microglia, and cytokine overexpression disrupt normal synaptic growth, pruning and function can potentially lead to reduced resiliency to future stressors and neuropsychiatric disorders. To stain for microglia morphology and activation status, we use ionized calcium binding adaptor molecule 1 (Iba1) and MER proto-oncogene tyrosine kinase (MerTK). The findings from this project can help uncover pathophysiological connection between ACEs and consequent neuropsychiatric disorders and thus the development of novel therapeutic approaches to prevent or mitigate the ACE-driven dire consequences.

Disclosures: **T. Supty:** None. **T.L. Cain:** None. **A. Dobard:** None. **K.M. Smith:** None.

Poster

PSTR019: Neuroinflammation: Microglia

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.02/C139

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: HK110-165

Title: The effects of alcohol on different areas of brain in rats

Authors: *J.-Y. WANG[1], S.-Y. CHEN[2];
[1]Dept Nursing (Basic Med. Sci), Hungkuang Univ., Taichung, Taiwan; [2]Nursing, Hungkuang Univ., Shalu, Taiwan

Abstract: Alcohol (EtOH) is considered to be one of the most commonly abused chemical. Excessive alcohol consumption induces neurological damage including change of neuroinflammatory response and impairment in learning and memory function. Neuroinflammation is accompany with neuronal injury and the activation of glial cells (including astrocytes and microglial cells). Evidence indicated that ethanol exposure induced microglial over activation to release inflammatory mediators including tumor necrosis factor (TNF-α) and nitric oxide (NO) and decreased the number of neurons in mice brain. However, some data indicated that the microglial activation was not positive correlation to neuroinflammation in

EtOH-induced neurodegeneration. Even though glial cells are very important constituents in the brain, but the results of investigation of EtOH in glial cells are not clear. Furthermore, the different areas of brain have different functions and sensitivity. The temporal lobe plays a role in memory. It is known that addition and CNS damage are causal factor. The nucleus ambiguous (NAc) has important effect on addition, and there is close relationship between NAc and prefrontal cortex, hippocampus, ventral tegmental area. In this study, we wanted to estimate the cell injury and the neuroinflammation following alcohol exposure of different brain areas in rats. Male SD rats fed with various concentration of alcohol for 1 week (Day 1 and 2: 1 %; Day 3 and 4: 5 %; Day 5, 6 and 7: 10 % alcohol). The diet of rats was restricted in order to decrease 20 % body weight. Then we started operating the behavioral experiment and estimated the memory functions by 8 arm maze. Rats were sacrificed after about 1 month and prepared brain section for immunocytostaining. The results of immunocytostaining of brain slices revealed that the number of neuron and astrocyte were decreased significantly (about 30 %); however, the activation of microglial cells was increased significantly (about 400 %) in alcohol treatment group of various brain area. The expression of TNF-α and iNOS were significant increased. We suggested that alcohol will impair the neuron and astrocyte, and alcohol will induce the activation of microglial cells to release inflammatory mediators. The inflammatory response in prefrontal cortex and hippocampus (CA1) were higher than other brain areas.

Disclosures: **J. Wang:** None. **S. Chen:** None.

Poster

PSTR019: Neuroinflammation: Microglia

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.03/C140

Topic: B.09. Glial Mechanisms

Support: NIH Grant 5P20GM103642
NIH-RISE 5R25GM061151-19

Title: Examining Glial Cell Mitochondrial Morphology and Drosophila Viability: Manipulating MARF to Explore Neuronal Function

Authors: *N. M. JIMENEZ-VIZCARRONDO[1], C. DEL VALLE-COLÓN[1], A. GHEZZI[1], E. BARNHART[2];
[1]Univ. of Puerto Rico, Río Piedras, Puerto Rico; [2]Columbia Univ., New York, NY

Abstract: Proper neuronal function requires high amounts of energy, primarily generated through mitochondrial oxidative phosphorylation (OXPHOS). Glial cells are thought to provide some metabolic support to mitochondria in neurons, specifically by shuttling a by-product of glycolysis, lactate, to the neurons. However, in vivo work has shown that knocking down lactate transporters in glial cells significantly reduces fly viability. Interestingly, glia are thought to only rely on glycolysis, it is commonly perceived that glial cells possess smaller mitochondria.

However, the Barnhart lab has recently shown that glial cells surprisingly contained large and highly branched mitochondria. However, scientists have yet to answer the significance of mitochondrial morphology in glial cells. Recently, the Barnhart lab has shown that glial cells surprisingly contained a high amount of large and highly branched mitochondria. I propose altering the morphology of the mitochondria in glial cells could also affect *Drosophila* viability and neuronal function. I want to understand the role of these big and branched mitochondria within the glial cells by genetically manipulating with the GAL4/UAS system where I am upregulating and downregulating Marf, a pro-fusion factor that regulates mitochondrial morphology, in *Drosophila melanogaster's* well characterized visual system. Additionally, I will introduce alcohol as a variable to assess its effects on glial-dependent neuroplasticity and mitochondrial function within glial cells, and how these changes can possibly alter the viability of the flies. Overexpression of Marf will lead to an enlarged mitochondria within glia, while employing RNAi knockdown will result in a reduction in size. Subsequently, I evaluated the outcomes of modulating MARF expression levels by fixing and staining *Drosophila* brains, followed by imaging using confocal microscopy. Lastly, scoring for viability and conducting behavioral assays to determine neuronal function was carried out. With this work, I aim to investigate how mitochondrial morphology in glial cells affects fly viability and behavior.

Disclosures: **N.M. Jimenez-Vizcarrondo:** None. **C. Del Valle-Colón:** None. **A. Ghezzi:** None. **E. Barnhart:** None.

Poster

PSTR019: Neuroinflammation: Microglia

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.04/C141

Topic: B.09. Glial Mechanisms

Support: RO1: AA027516
T32: AA026577

Title: Minocycline Reduces Binge Ethanol Consumption in C57Bl6/J Mice

Authors: *S. SCHRANK[1], N. YUNUS[2], J. P. SEVIGNY[3], K. VETTER[4], M. VALCHINOVA[5], O. D. AGUILAR[6], V. ILY[4], D. R. SPARTA[7];
[1]Univ. of Chicago at Illinois, Chicago, IL; [2]Univ. of Illinois-Chicago, Chicago, IL; [3]Psychology, Univ. of Illinois Chicago, Chicago, IL; [4]Univ. of Chicago Illinois, Chicago, IL; [5]Univ. of Illinois at Chicago, chicago, IL; [6]UIC Psychology Dept., Univ. of Illinois at Chicago, Chicago, IL; [7]Psychology, UIC, Chicago, IL

Abstract: Alcohol use disorder (AUD) is as pervasive as it is devastating, effecting 10.5% of Americans over the age of 12. While not every person who consumes alcohol will develop AUD, it has been identified that binge drinking behavior (4 or 5 drinks per outing for woman or man respectively) predisposes AUD development. One frontline therapeutic intervention for AUD is

naltrexone, which intriguingly in the (+)-opioid inactive isomer state antagonizes the innate immune associated Toll-like Receptor 4 (TLR4). Therefore, we explored the ability of the anti-inflammatory drug minocycline to decrease binge ethanol consumption. In a 5-week ABABA design, daily minocycline IP treatment (50mg/kg) consistently reduced ethanol intake in treated groups but not in saline IP controls. Behavior testing 24 hours after the last drinking and injection day on treated weeks revealed no relative changes between groups on either Open field or EPM on anxiety like behavior suggesting that minocycline treatment does not increase anxiety or affect ambulatory behavior during alcohol abstinence. In a separate cohort of animals, mice were given intermittent access to sucrose for 4 days in the same time frame as the DID experiments, where animals were treated with either saline or minocycline on day 3 and day 4 to determine if minocycline would affect consumption of natural rewards and found no effect on consumption. Future studies will evaluate if minocycline given after DID reduces anxiety-like phenotypes which would suggest that minocycline treatment may reduce the negative affective state precipitated by alcohol abstinence. Minocycline will also be evaluated for its ability to produce a general anhedonia effect like naltrexone, where then we will interrogate how inflammation consequent of alcohol interacts with brain reward systems. Taken together, this suggests that minocycline may be a viable therapeutic agent for treating AUD.

Disclosures: **S. Schrank:** None. **N. Yunus:** None. **J.P. Sevigny:** None. **K. Vetter:** None. **M. Valchinova:** None. **O.D. Aguilar:** None. **V. Ily:** None. **D.R. Sparta:** None.

Poster

PSTR019: Neuroinflammation: Microglia

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.05/C142

Topic: B.09. Glial Mechanisms

Support: T32: AA026577
RO1: AA027516

Title: Methods in Microglial Morphology Analysis: Beyond ImageJ Plugins

Authors: ***N. YUNUS**[1], S. SCHRANK[2], J. P. SEVIGNY[3], K. VETTER[4], M. VALCHINOVA[5], O. D. AGUILAR[6], V. ILY[4], A. T. KEINATH[3], D. R. SPARTA[7];
[1]Psychology, Univ. of Illinois-Chicago, Chicago, IL; [2]Univ. of Chicago at Illinois, Chicago, IL; [3]Psychology, Univ. of Illinois Chicago, Chicago, IL; [4]Univ. of Illinois-Chicago, Chicago, IL; [5]Univ. of Illinois at Chicago, chicago, IL; [6]UIC Psychology Dept., Univ. of Illinois at Chicago, Chicago, IL; [7]Psychology, UIC, Chicago, IL

Abstract: Alcohol use disorder (AUD) is a common and devastating disorder effecting upwards of 29 million people in the United States in 2022. The etiology of AUD is complicated, likely involving environmental, genetic, and social components, and relatively new and under-explored contribution of inflammatory processes within the CNS. While the peripheral immune effects of

AUD have clearly demonstrated a role of inflammation in liver associated pathology, to what extent inflammation effect alcohol drinking behaviors by acting on associated brain regions is not well characterized. Microglia are the resident immune cells of the brain and are intimately involved in the neuroimmune response to alcohol. Microglia are capable of dynamic responses to various immunological stimuli, and when activated can rapidly change their behavior to perform effector functions such as increasing production of proinflammatory cytokines, increasing phagocytic ability, increasing reactive oxygen or reactive nitrogen species, etc. Within their dynamism, it is possible to closely examine the morphology of microglia to infer their behavior, as microglia responding to inflammatory stimuli typically retract processes and increase soma size as a product of changing their function from one of surveillance and support to one initiating an immune response. Here, we demonstrate a novel technique to examine microglia morphology after alcohol consumption in the drinking in the dark (DID) paradigm that runs through MATLAB. This MATLAB code is capable of loading in z-stack confocal images, identifying microglia contained within the image stack, and then 2D skeletonizing the glia, and then analyzing various morphological features (number of branch points, total area of branches, mean branch length, branch depth, and cell body size) in a semi-automated and non-biased fashion. Utilizing the Cx3Cr1-GFP mouse line, we were able to assess microglial activation states within the CeA after repeated cycles of DID drinking with and without treatment of the potent anti-inflammatory drug minocycline, where it was observed that repeat DID cycles were associated with changes in microglial morphology including a reduction in branch number, branch area, and microglial soma size. Minocycline treatment was unable to rescue changes in branch number or branch size, but instead was associated with normalizing microglia soma hypertrophy. With the creation of this tool, we hope to increase the speed, efficiency, and accuracy with which microglia morphology is analyzed to aid in the detection and quantification of inflammation with the CNS.

Disclosures: **N. Yunus:** None. **S. Schrank:** None. **J.P. Sevigny:** None. **K. Vetter:** None. **M. Valchinova:** None. **O.D. Aguilar:** None. **V. Ily:** None. **A.T. Keinath:** None. **D.R. Sparta:** None.

Poster

PSTR019: Neuroinflammation: Microglia

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.06/C143

Topic: B.09. Glial Mechanisms

Support: NIAAA R01AA023797

Title: Interaction of ethanol and polygenetic background in Alcohol Use Disorder in human iPSC derived neural co-culture and 3D organoid system

Authors: ***X. LI**[1], J. LIU[2], A. J. BORELAND[4], S. KAPADIA[5], A. KREIMER[3], J. DUAN[6], R. P. HART[7], Z.-P. PANG[8];

[1]Rutgers, New Brunswick, NJ; [2]Dept. of Biochem. and Mol. Biology, Rutgers, The State Univ. of New Jersey, 604 Allison Road, Piscataway, NJ, 08854, Avenel, NJ; [3]Dept. of Biochem. and Mol. Biology, Rutgers, The State Univ. of New Jersey, 604 Allison Road, Piscataway, NJ, 08854, New York, NY; [4]Neurosci. and Cell Biol., CHINJ, Rutgers Univ., Highland Park, NJ; [5]The Child Hlth. Inst. of New Jersey, New Brunswick, NJ; [6]NorthShore Univ. HealthSystem/University of C, Evanston, IL; [7]Cell Biol. & Neurosci., Rutgers, The State Univ. of New Jersey, Piscataway, NJ; [8]Child Hlth. Inst. of New Jersey, Rutgers Univ., New Brunswick, NJ

Abstract: Alcohol exerts a range of effects on the human brain, including alterations in neurotransmitter release and neuroinflammation, which are implicated in the development and progression of alcohol use disorders (AUD). Genome-wide association studies (GWAS) have identified numerous gene variants associated with AUD. Integrating these variants by creating polygenic scores (PGS) offers insights into genetic susceptibility to AUD. However, the molecular implications of these PGS remain underexplored. Neuroimmune interactions, especially between microglia and neurons, are increasingly recognized as significant contributors to AUD pathophysiology. We investigated the interaction between AUD PGS and ethanol in a human microglia-neuron coculture and a 3D organoid system derived from iPSCs of individuals with high- or low-PGS of AUD. Transcriptomic analysis of microglia revealed differential expression of genes related to the MHCII complex and phagocytosis following ethanol exposure. Unlike low-PGS microglia, high-PGS microglia exhibited increased phagocytosis in both fluorescent zymosan bioparticles and synaptosomes after exposure to ethanol. Additionally, in microglia-neuron cocultures, we observed a reduction in synapse numbers and decreased frequencies of miniature excitatory postsynaptic currents in co-cultures with HPRS microglia, indicating potential excessive synapse pruning by high PGS microglia upon alcohol induction. Currently, we are investigating microglia-neuron interaction in a 3D organoid model. We hope to provide insights into the intricate relationship between AUD PGS, ethanol, and microglial function, potentially influencing neuronal functions in developing AUD.

Disclosures: **X. Li:** None. **J. Liu:** None. **A.J. Boreland:** None. **S. Kapadia:** None. **A. Kreimer:** None. **J. Duan:** None. **R.P. Hart:** None. **Z. Pang:** None.

Poster

PSTR019: Neuroinflammation: Microglia

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.07/C144

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NINDS R01 NS121692
NIH/NINDS 1R01 NS124226
DOD/CDMRP/NETP/SIA W81XWH2210608

Title: Pathological αSyn disrupts the nuclear pore complex in models of neuroinflammation and dopaminergic neurodegeneration

Authors: *G. S. RICHARDSON[1,2,3], C. D. MILLER[1,4], Z. RIAZ[1,5], G. ZENITSKY[1,5], H. JIN[5,1], V. ANANTHARAM[1,5], A. KANTHASAMY[5,1], A. G. KANTHASAMY[1,5];
[1]Isakson Ctr. for Neurolog. Dis. Res., [2]Psychology, [3]Biol., [4]Biochem. and Mol. Biol., [5]Physiol. and Pharmacol., Univ. of Georgia, Athens, GA

Abstract: Parkinson's disease (PD), dementia with Lewy bodies (DLB) and mixed etiology dementias (MEDs) are characterized by the accumulation and release of abnormal aggregates of misfolded α-synuclein (αSyn) from neurons. These aggregates are known to activate resting microglia, transforming the structural and functional properties of cells. Mechanistically, aggregated αSyn stimulation in microglia induces neuroinflammation by activating a myriad of pathophysiological processes including cytokine and chemokine gene upregulation, ROS/RNS generation and phagocytosis. Despite vast structural and functional changes occurring in activated microglia, biochemical mechanisms underlying the immune transformation of glial cells during dopaminergic neurodegeneration have yet to be defined. As nuclear pore complexes (NPCs) serve as a gateway for the nucleocytoplasmic transport (NCT) of key transcription factors and mRNAs involved in neuroinflammation, herein, we examined the structural and functional features of NPCs as they relate to PD. Excitingly, we found that a large portion of nucleoporin (NUP) proteins are downregulated in a rotenone-induced oxidative stress model of dopaminergic neurodegeneration. Among them are NUP50 and NUP153, which are basket NUPs involved in transporting proteins and RNA species. Based on this finding, we further examined whether the NPC and related proteins are dysregulated in an αSyn-induced model of microglial activation and neuroinflammation. We found that NUP153 and NUP50 are significantly downregulated in C20 human microglial cells following αSyn stimulation. In future studies, we will investigate the functional significance of dysregulated selective NUPs in disturbing the microglial NCT mechanism, specifically as it relates to the expression and localization of proinflammatory protein transcripts. Collectively, this study builds on our previous work supporting a role for NPC dysregulation in the molecular mechanisms underpinning both neurodegenerative and neuroinflammatory processes.

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Poster

PSTR019: Neuroinflammation: Microglia

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.08/C145

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01GM128183 to U.R.

Title: The $GABA_A$ receptor α5-selective positive allosteric modulator, MP-III-022, attenuates postoperative cognitive impairments in aged mice via distinct mechanisms

Authors: *J. LYU[1,2], R. NAGARAJAN[3], M. KAMBALI[3], M. WANG[3,4], D. SHARMIN[5], J. M. COOK[5], U. RUDOLPH[3];
[1]Neurosci. Program, Univ. of Illinois Urbana-Champaign, Urbana, IL; [2]Comparative Biosciences, University of Illinois Urbana-Champaign, Urbana, IL; [3]Comparative Biosci., Univ. of Illinois Urbana-Champaign, Urbana, IL; [4]Neuroscience Program, University of Illinois Urbana-Champaign, Urbana, IL; [5]Chem. and Biochem., Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: Postoperative neurocognitive disorder (poNCD), i.e., cognitive deficits persisting more than one month after surgery, is a relatively common complication among elderly human patients. Studies have shown that GABAergic neurotransmission may be diminished in aged brains, potentially contributing to cognitive dysfunction. Previously, we found that MP-III-022 can block the development of poNCD in aged mice. However, since MP-III-022 has been administered throughout the experiments previously, the timeline of its action was unknown. We hypothesized that MP-III-022 both inhibits surgery-induced microglial activation and restores impaired function of the α5-$GABA_A$ receptor system in the aged brain. To determine the critical period for intervention, we limited the administration of MP-III-022 to the "early time window" (2 days before to 3 days after surgery), which would be expected to block microglial activation, or to the "late time window" (4-20 days post-surgery), which would be expected not to block microglial activation but to restore the age-related reduction of activity of the α5-$GABA_A$ receptor system. Our research utilized two types of mice: mice with partial ablation of dentate hilar somatostatin interneurons, modeling hippocampal aging, and chronologically aged mice. We observed that laparotomy compromised cognitive function in both types of mice, as evidenced by performance in novel object recognition, water maze, and contextual fear conditioning tests. Notably, MP-III-022 attenuated postoperative cognitive deficits when administered both in the early (i.e., perioperative) and the late (i.e., postoperative) time windows. Additionally, laparotomy-induced microglial activation was blocked by the administration of MP-III-022 in the early (perioperative) time window and laparotomy-induced reductions in dendritic spine density occurred primarily in the late (postoperative) time window. These findings suggest that positive allosteric modulation of α5-containing $GABA_A$ receptors improves laparotomy-induced cognitive deficits via multiple distinct mechanisms. Positive allosteric modulation of α5-$GABA_A$ receptors offers a promising avenue for preventing or reversing cognitive impairments induced by surgery and may thus represent a novel strategy for the prevention or treatment of poNCD in elderly people.

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Poster

PSTR019: Neuroinflammation: Microglia

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.09/C146

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: RF1AG028271
R03AG067061
R21AG071133

Title: Exploring Potential Mechanisms of Post-Surgical Morphine Associated with Persistent Spatial Memory Deficits in Aged Females Rats

Authors: *B. ALVAREZ[1], S. MUSCAT[2], J. DEMARSH[3], M. N. BETTES[4], M. BUTLER[5], D. KOLONAY[6], H. SANDERS[3], K. K. BASKIN[6], R. M. BARRIENTOS[7];
[1]The Ohio State Univ. Neurosci. Grad. Program, Columbus, OH; [2]The Ohio State Univ., Columbus, OH; [3]Ohio State Univ., Columbus, OH; [4]The Ohio State Univ., Ohio State University, OH; [5]Col. of Med., The Ohio State Univ., Columbus, OH; [6]Physiol. and Cell Biol., The Ohio State Univ., Columbus, OH; [7]Inst. for Behavioral Med. Res., The Ohio State Univ., Columbus, OH

Abstract: Background: Post-operative cognitive dysfunction (POCD) involves several types of cognitive impairments including memory deficits. These deficits are observed after various types of surgical procedures, persist months after surgery, and are accompanied by elevated risk of mortality and dementia, predominantly in older individuals (>65 years old). Approximately 25% of these individuals are diagnosed with POCD after surgery, with female patients being twice as susceptible than males, yet POCD research remains male centric. Aging is also known to alter sex hormones (i.e., menopause), which could factor into why females show greater susceptibility to POCD. Here, we examined POCD in young and aged (acyclic) female rats. We hypothesized that the combination of aging, laparotomy, and morphine would impair hippocampal- dependent memory through alterations in neuroinflammation, mitochondrial function, and reactive oxygen species (ROS). **Methods:** To determine these differences, we performed either sham surgeries or laparotomies on young adult (3 mos) and aged (22 mos) female rats, followed by 7 days of saline or morphine (2mg/kg, i.p., 2x/day). Two weeks post-surgery, several behavioral task were conducted. Neuroinflammatory markers (i.e., IL-4, IL-1β, IL-6, IL-10, & TNF-α) and ROS, were measured in the hippocampus via ELISA. Mitochondrial respiration in hippocampus was also assessed via the Seahorse Analyzer. **Results:** We found that all 3 inflammatory factors (i.e., aging, morphine, and surgery) were necessary to impair spatial memory. Rats in this group also exhibited mitochondrial dysfunction and exaggerated levels of ROS in the hippocampus. Regardless of age, surgery dysregulated cytokines in the hippocampus. This inflammatory dysregulation resolved by 4 weeks post-surgery in the young but not the aged female rats. **Conclusion:** Although aged female rats present with hippocampal-dependent memory deficits that are similar to males, the mechanisms underlying these behavioral impairments are subtly different.

Disclosures: B. Alvarez: None. **S. Muscat:** None. **J. DeMarsh:** None. **M.N. Bettes:** None. **M. Butler:** None. **D. Kolonay:** None. **H. Sanders:** None. **K.K. Baskin:** None. **R.M. Barrientos:** None.

Poster

PSTR019: Neuroinflammation: Microglia

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.10/C147

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant AA029674

Title: Effects of novel beta-lactam, MC-100093, and ceftriaxone on astrocytic glutamate transporters and neuroinflammatory factors in nucleus accumbens of C57BL/6 mice exposed to escalated doses of morphine

Authors: *Y. SARI[1], M. A. ABOU-GHARBIA[2], W. E. CHILDERS, Jr.[3], S. ALSHARARI[4], F. ALASMARI[5];
[1]Univ. of Toledo Col. of Pharm. and Pharmaceut. Sci., Toledo, OH; [2]Pharmaceut. Sci., Temple Univ., Philadelphia, PA; [3]Temple Univ., Philadelphia, PA; [4]Pharmacol. & Toxicology, King Saud Univ., Richmond, Saudi Arabia; [5]Pharmacol. and Toxicology, King Saud King, Riyadh, Saudi Arabia

Abstract: Chronic use of opioid has been a major health problem. Studies from ours and other groups showed that chronic exposure to opioids downregulated astrocytic glutamate transporter 1 (GLT-1), which regulates the majority of glutamate uptake. In addition, our lab revealed that beta-lactam antibiotic, ceftriaxone, attenuated hydrocodone-induced downregulation of the expression of GLT-1 and cystine/glutamate antiporter (xCT) in central reward brain regions. In this study, we investigated the effects of escalating doses of morphine and tested the efficacy of novel synthetic non-antibiotic drug, MC-100093, as well as ceftriaxone in attenuating the effects of exposure to escalating doses of morphine in the expression of GLT-1, xCT, and neuroinflammatory factors (IL-6 and TGF-β) in the nucleus accumbens (NAc). This study also investigated the effects of morphine and these beta-lactams in locomotor activity, percentage of spontaneous alternation behavior (%SAP) and number of entries in Y maze since opioids have effects in locomotor sensitization. Mice were exposed to morphine (20 mg/kg, i.p.) on days 1, 3, 5, 7 and a higher dose of morphine (150 mg/kg, i.p.) on day 9, and they were then behaviorally tested and euthanized on Day 10. Western blot analysis showed that exposure to escalated doses of morphine downregulated GLT-1 and xCT expression in the NAc, and both MC-100093 and ceftriaxone attenuated these effects. In addition, morphine exposure increased IL-6 mRNA and TGF-β mRNA expression, and MC-100093 and ceftriaxone attenuated only the effect on IL-6 mRNA expression in the NAc. Furthermore, exposures to escalated doses of morphine induced an increase in distance travelled, and MC-100093 and ceftriaxone attenuated this effect. In addition, exposure to escalated doses of morphine decreased the % SAP and increased the number of arm entries in Y maze, however, neither MC-100093 nor ceftriaxone had any attenuating effect. Our findings showed for the first time that the novel beta-lactam, MC-100093, as well as ceftriaxone attenuated morphine-induced downregulation of GLT-1 and xCT expression and the increase in neuroinflammatory factor, IL-6, as well as the hyperactivity. These findings revealed the beneficial therapeutic effects of the novel synthetic beta-lactam,

MC-100093, as well as ceftriaxone against the effects of exposure to escalated doses of morphine.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.01/C148

Topic: C.09. Stroke

Support: CIHR PS 180244

Title: Investigating different neuromodulators and their effects on neutrophil adhesion molecule expression and adherence in ischemic stroke

Authors: *A. STPIERRE[1], T. JOY[2], R. BOGHOZIAN[2], S. FALCIONE[2], R. TODORAN[1], M. C. REAL[2], M. CLARKE[2], Y. ZHANG[1], I. R. WINSHIP[3], G. C. JICKLING[4];
[1]Neurosci. and Mental Hlth. Institute, Fac. of Med. and Dent., [3]Psychiatry, [4]Medicine/Neurology, [2]Univ. of Alberta, Edmonton, AB, Canada

Abstract: Cerebral ischemia evokes a peripheral inflammatory response that includes activation of neutrophils. Neutrophils may become activated and adhere to the cerebral microvasculature, leading to neutrophil stalls that impede blood flow. The presence of these stalls contributes to ongoing penumbral injury resulting in greater tissue damage. Futile recanalization occurs when the occluded blood vessels are patent, but no reperfusion results. Taken together, these factors prevent stroke patients from attaining successful functional outcomes. Endothelin-1 (ET-1) is a vasoactive peptide that increases in plasma during stroke and may activate neutrophils, increasing their adherence. Antagonizing ET-1 may improve blood flow by increasing dilation and reducing neutrophil stalls. This study utilized both selective ETA receptor (BQ-123, Sitaxentan) and dual ETA/ETB receptor (Macitentan) antagonists to determine the potential therapeutic benefits of ET-1 on neutrophil adhesion in stroke. We investigated how ET-1 alters the expression of adhesion molecules (ICAM-1, CD18, CD11b) on neutrophils and whether ET-1 and its inhibition may alter neutrophil adherence to an endothelial layer. Blood samples from healthy controls and stroke patients, as well as cultured neutrophils (HL-60 cell line), were treated with and without ET-1 antagonists, including BQ-123, Sitaxentan, and Macitentan. Neutrophil adhesion molecule expression of ICAM-1, CD18, and CD11b were measured by flow cytometric analysis. An hCMEC cell line was cultured to create an endothelial layer for a neutrophil binding assay. The endothelial layer was treated with and without ET-1 antagonists to quantify adherence of neutrophils after ET-1 stimulation and blockade. Flow cytometric analysis shows adhesion molecules ICAM-1, CD18, and CD11b are all highly expressed on the surface of neutrophils and remain highly expressed when stimulated with ET-1. CD18 and CD11b

expression appear to be more greatly influenced by ET-1 antagonization. Ongoing work is evaluating ET-1 stimulation on neutrophil binding to an endothelial layer. Preliminary results demonstrate less neutrophil binding when treated with the dual ETA/B receptor antagonist Macitentan. We expect that the inhibition of ET-1 with BQ-123, Sitaxentan, or Macitentan will decrease adhesion molecule expression. Blocking the ET-1A receptor may induce vasodilation by acting on endothelial cells. Determining whether blocking ET-1 also affects neutrophil adhesion molecule expression and adherence would identify an additional potential therapeutic benefit of this treatment for acute stroke.

Disclosures: A. StPierre: None. **T. Joy:** None. **R. Boghozian:** None. **S. Falcione:** None. **R. Todoran:** None. **M. C. Real:** None. **M. Clarke:** None. **Y. Zhang:** None. **I.R. Winship:** None. **G.C. Jickling:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.02/C149

Topic: C.09. Stroke

Support: CIHR PS 166144

Title: Promoting patterns of gene expression supporting neuroplasticity via cortical microinjections of pleiotrophin in a mouse model of ischemic stroke

Authors: *R. BERTENSHAW[1], C. S. TANASE[1], M. D. CLARKE[2], Y. MA[3], P. C. KENT[3], T. JOY[2], G. C. JICKLING[2], I. R. WINSHIP[3];
[1]Neurosci. and Mental Hlth. Inst., [2]Med., [3]Psychiatry, Univ. of Alberta, Edmonton, AB, Canada

Abstract: Ischemic strokes are one of the most prevalent contributors to death and disability among adults worldwide and result from a reduction in blood flow in the brain. An emerging approach in stroke research involves modulating neuroplasticity to heighten the central nervous system's (CNS) innate ability to recover following an injury. One way to increase the adaptive plasticity of the CNS is to modulate the inhibitory environment induced by chondroitin sulfate proteoglycans (CSPGs) in the extracellular matrix (ECM). A neurotrophic factor called pleiotrophin (PTN) has been found to interact with CSPGs and promote synaptogenesis as well as the formation of growth processes without the need for enzymatic CSPG degradation. In this study, we investigated the resulting changes in gene expression following the administration of PTN protein in cerebral cortices in mice after ischemic strokes. Photothrombosis was used to induce ischemic strokes centred around the right sensorimotor cortex in adult C57BL6/J mice (n = 18), after which the mice received a cortical microinjection of recombinant PTN protein the day after. One week following stroke induction, the mice were euthanized, and RNA was extracted from the brain tissue surrounding the ischemic area. The tissue samples were sent to Genome Quebec for bulk RNA sequencing, and bioinformatics analyses were performed using

the Partek Genomics Suite and the DESeq2 Bioconductor packages on R. We found evidence that PTN causes differential expression when administered in stroke animals specifically, implying a combinatorial effect. We also found an overrepresentation of developmental pathways and proteoglycan ECM components in the upregulated genes in the stroke mice that received PTN injections, some of which include the proteins vcan, sdc3, nrp2, and igf2. Meanwhile, we found an overrepresentation in pathways involved with the modulation of synaptic integrity in the downregulated genes, including proteins like psd95, sap90, camk2a, and shank1. We postulate that a downregulation in genes involving synaptic integrity may allow for new synapses to form that could help in functional recovery post-stroke. Together, these findings provide evidence that PTN may have a beneficial effect after stroke by promoting processes tied to neuroplasticity.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.03/C150

Topic: C.09. Stroke

Support: Wallonie-Win4Company n°8724 STROMA

Title: Improvement of neurological outcomes following Stroke or traumatic brain injury in mice treated with a novel first-in-class compound

Authors: *Q. MARLIER, M. GILSOUL, M. WOZNIAK, A. BOREUX, D. MOSCA, A. RIVES, P. ATTALI, S. SILVENTE, P. LEFEBVRE, N. CARON;
Dendrogenix, Liège, Belgium

Abstract: Stroke and Traumatic brain injury (TBI) are leading causes of long-term disability and mortality worldwide. New strategies to mitigate the devastating consequences of these insults are urgently needed. In our study, we employed a combination of in vitro and in vivo models to replicate the pathophysiology of ischemic stroke and traumatic brain injury. Specifically, we used an oxygen glucose deprivation model (OGD) in vitro to stimulate ischemic condition in primary culture of mice cortical cells. We also used a middle cerebral artery occlusion (MCAO) model in vivo to induce ischemic stroke in male mice. Additionally, we used a controlled cortical impact (CCI) model in vivo to mimic TBI also in male mice. This comprehensive approach allowed us to investigate the therapeutic potential of our novel compound, in improving neurological outcomes post-stroke and TBI in murine models. Our results demonstrate that our treatment restored 36,8% of the living neuronal cells in culture following 4h of OGD and 24h of reperfusion. To Transpose these data in vivo, we measured by Triphenyl tetrazolium chloride (TTC) staining the volume of the ischemic insult 48 hours following 1h of MCAO. We observed

that our compound reduces the size of the lesion by 70%. Behavioral assessments have been performed before TTC staining to measure spontaneous locomotion (open field) and motor coordination (rotarod). Our molecule increased mice speed by 47% and restored motor coordination up to 73% compared to control mice. In parallel, the motor function was evaluated in mice 7, 14, 21 and 22 days following CCI. Our drug improved by 36% motor coordination along time compared to control CCI mice. These data indicate that our new compound act positively on neuronal circuitry responsible for motor behavior in a context of ischemic and/or traumatic neuronal accident. These results highlight promising neurorestorative properties of this new molecule and suggest its potential as a therapeutic agent for stroke and TBI patients. Further investigation in preclinical and clinical settings is warranted to elucidate its full therapeutic potential and pave the way for novel treatment strategies in neurological disorders.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.04/C151

Topic: C.09. Stroke

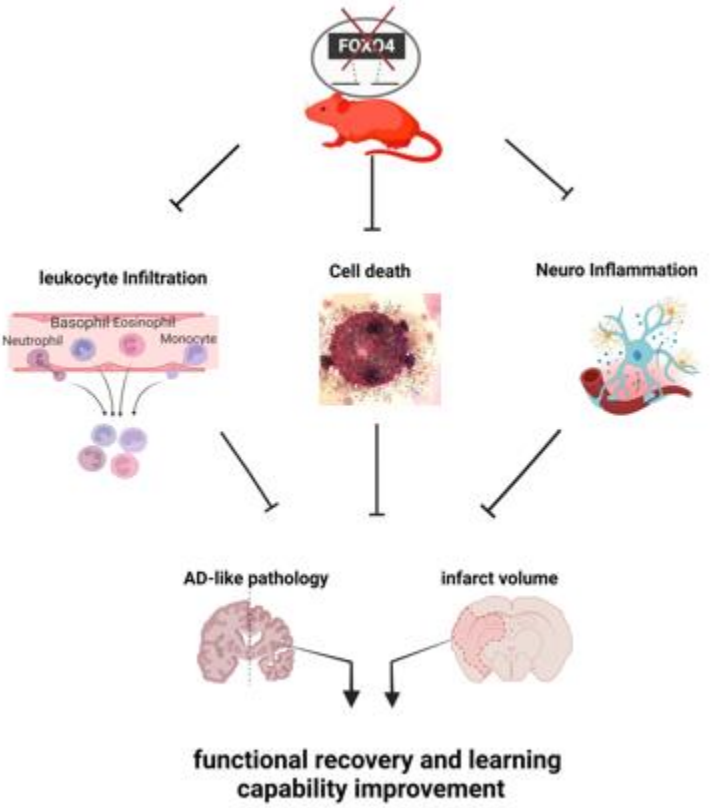
Support: NIH Grant R01NS124846

Title: Inhibition of FOXO4 reduces ischemic stroke-caused injury and improves neurological outcomes after cerebral ischemia-reperfusion in mice.

Authors: *Y. ASADI[1], A. DWAMENA[2], E. A. GILSTRAP[3], H. WANG[2];
[1]TTUHSC, Lubbock, TX; [3]Pharmacol. and Neurosci., [2]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Background: Transcriptional regulation is one of the most influential mechanisms regulating cell function. In ischemia/reperfusion (I/R) conditions, FOXO transcriptional factors serve as a critical regulator in vivo and in vitro. From previous data, FOXO4 works as an enhancer for inflammation and oxidative stress in non-brain tissues, indicating that downregulation of the FOXO4 may be protective in I/R-induced injury. However, this possibility has not been tested in the cerebral I/R condition. **Method:** 2-3 months of FOXO4 knockout (KO) and wild-type (WT) mice were subjected to the middle cerebral artery occlusion for 1 hour prior to reperfusion. The animals were sacrificed after 24 hours or 48 hours before their brain was collected for TTC staining to examine brain injury (at 24 hours), immunohistochemical staining to assess astrocytes and microglia (at 48 hours), and the levels of protein expression to evaluate proinflammatory cytokines and Alzheimer's disease-like pathologies (at 48 hours). Alternatively, animals were allowed to survive for 1-10 days following I/R to test their functional recovery.

Result: KO of FOXO4 reduced the infarct volume and decreased neurological deficits compared to WT mice, suggesting that disrupting FOXO4 attenuates I/R-induced brain injury and promotes functional recovery after I/R. KO mice showed better learning, memory, and neurological function than the WT mice. Immunohistochemical staining of astrocytes and microglia revealed that KO brains showed decreased astrocytes and microglia in the peri-infarcted area two days after I/R. Western blot analysis of proinflammatory cytokines, such as Il-6, TNF α, and IL-1 β, indicated decreased levels of proinflammatory cytokines after two days following I/R. Moreover, we found reduced protein levels of amyloid β, amyloid precursor protein, tau, and P-tau in the KO mouse brain compared to the WT mouse brain two days following I/R. **Conclusion:** Disrupting FOXO4 expression is neuroprotective, which could be a promising therapeutic strategy against ischemic stroke and AD-like pathology after stroke.



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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.05/C152

Topic: C.09. Stroke

Support: AHA 23TPA1068534

Title: Sex and age-dependent effects of miR-15a/16-1 antagomir on ischemic stroke outcomes

Authors: *X. HUANG[1], S. LI[1,2], N. QIU[1,2], T. XIONG[1], J. XUE[1,2], K. YIN[1,2];
[1]Dept. of Neurol., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [2]Geriatric Research, Educ. and Clin. Ctr., Veterans Affairs Pittsburgh Healthcare Syst., Pittsburgh, PA

Abstract: Ischemic stroke is a serious disease that causes severe disability in humans worldwide. There is increasing evidence implicating microRNAs (miRs) are involved in the pathophysiology of ischemic stroke. Studies have shown that miR-15a/16-1 is abnormally expressed in brains after ischemic stroke, and its upregulation may increase ischemic damage. Sex and age factors are known outcome modifiers. Here, we investigated the potential of miR-15a/16-1 antagomir to prevent cerebral ischemia/reperfusion (I/R) injury, and explored its dependence on sex and age and its potential mechanism. Young (3 months) and aged (18 months) male and female C57/BL mice underwent 1h middle cerebral artery occlusion and 3-7d reperfusion (tMCAO). MiR-15a/16-1 antagomir or control antagomir was administered via tail vein 2 hours post-MCAO. Neurobehavioral testing and infarct volume assessment were performed on day 3 and 7. Compared to controls, antagomir treatment significantly improved neurobehavioral outcomes and reduced infarct volume in tMCAO mice at day 7, with a more pronounced effect in young animals. Notably, young female mice exhibited superior survival and sensorimotor function compared to young male mice. Mechanistically, miR-15a/16-1 antagomir may regulate genes involved in apoptosis, inflammation, and oxidative stress. Sex and age-dependent expression of miR-15a/16-1 and its targets likely underlie the observed variations. This study highlights the potential of miR-15a/16-1 antagomir as a therapeutic approach for ischemic stroke and suggests that sex and age should be considered when developing miR-based therapeutic strategies.

Disclosures: X. Huang: None. **S. Li:** None. **N. Qiu:** None. **T. Xiong:** None. **J. Xue:** None. **K. Yin:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.06/C153

Topic: C.09. Stroke

Support: HL141998
HL141998-01S1
AA025744
AA026708
AA025744-02S1
P20GM12130

Title: Enhancing Stroke Outcomes Through Endothelial-Specific Deletion of Autotaxin

Authors: *M. PANCHATCHARAM[1], V. MANIKANDAN[2], S. MANIKANDAN[2], S. MIRIYALA[2];
[1]Louisiana State Univ. Hlth. Scienc Pharmacoloy, Toxicology & Neurosci., Shreveport, LA;
[2]A.T. Still Univ., Kirksville, MO

Abstract: Introduction: Autotaxin (ATX) is an extracellular enzyme that exacerbates vascular pathologies via its product, lysophosphatidic acid (LPA). This enzyme is crucial in increasing vascular permeability and disrupting the blood-brain barrier (BBB), factors that aggravate ischemic stroke. Our study investigates the effects of endothelial-specific deletion of ATX on stroke outcomes, focusing on the ATX-LPA signaling pathway.Hypothesis: We hypothesize that deleting ATX specifically in endothelial cells mitigates adverse stroke outcomes by reducing vascular permeability and improving cerebral blood flow, thus preserving BBB integrity.Methods: Using a mouse model with endothelial-specific ATX deletion (ERT2 ATX-/-), we evaluated ATX activity and vascular permeability via AR2 probe and Evans Blue staining, respectively. Cerebral blood flow was monitored post-stroke using laser speckle imaging. We also assessed endothelial permeability, mitochondrial bioenergetics, and ATX activity through electrical cell-substrate impedance sensing (ECIS), Seahorse analysis, and fluorescence assays, respectively. Additionally, the effects of LPA receptor inhibitors and ATX inhibition on endothelial function were tested.Results: The ERT2 ATX-/- mice exhibited significant improvements in stroke outcomes, such as reduced permeability and infarct volume, and better-preserved cerebral blood flow compared to control I/R mice. LPA was found to worsen endothelial permeability and mitochondrial dysfunction, which were ameliorated by LPA receptor inhibitors and ATX inhibition, underscoring the harmful impact of the ATX-LPA axis on BBB and endothelial health following ischemic stroke.Conclusion: Endothelial-specific deletion of ATX significantly reduces BBB disruption and enhances stroke outcomes by curbing the negative effects of the ATX-LPA axis on vascular permeability and endothelial integrity. These findings support targeting the ATX-LPA signaling pathway as a viable therapeutic strategy to lessen the consequences of ischemic stroke. Further research is warranted to explore the mechanisms of BBB disruption and the therapeutic potential of inhibiting ATX-LPA signaling in stroke management.

Disclosures: M. Panchatcharam: None. **V. Manikandan:** None. **S. Manikandan:** None. **S. Miriyala:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.07/

Topic: C.09. Stroke

Title: DJ-1 oxidation inhibitor reduces neuronal ferroptosis after experimental intracerebral hemorrhage by maintaining the interaction between DJ-1 and S-adenosylhomocysteine hydrolase-like protein 1

Authors: *C. ZHANG;
Dept. of Surgery, Sch. of Clin. Med., LKS Fac. of Med., The Univ. of Hong Kong, Hong Kong, China

Abstract: Intracerebral haemorrhage (ICH), the second-most common subtype of stroke, has a high disability rate due to the post-ICH brain damage and limited treatments. DJ-1, a cytoprotective protein, can be oxidised and lose its protective functions. Our previous study, either *in vitro* or *in vivo*, found dramatically increased oxidised DJ-1 without significant changes in DJ-1 expression. In addition, behavioural tests showed that the DJ-1 oxidation inhibitor, DJ-1-binding compound 23 (Comp-23), reduced sensorimotor functional deficits after ICH. Staining of the mouse brain, including Luxol fast blue staining, NeuN immunostaining and Nissl staining, and transmission electron microscopy (TEM) on the mouse cervical spinal cord, demonstrated significantly decreased post-ICH demyelination and neuronal death in the Comp-23 treatment group. Based on these preliminary findings, this study aimed to explore the post-ICH neuroprotective mechanisms of the Comp-23. We induced ICH *in-vitro* models in HT-22 neuronal cell line and mature primary neurons by hemin and established *in-vivo* ICH mice model by intra-striatal collagenase injection. Ferroptosis is one of the central neuronal deaths after ICH. Cell viability assay, Live/Dead cell assay, Liperfluo staining, and FerroOrange staining in the *in-vitro* model and MDA assay in the *in-vivo* model showed that Comp-23 significantly reduced neuronal death and cell lipid peroxidation after ICH. Moreover, TEM on the *in-vivo* model perihematomal region and *in-vitro* model treated with Comp-23 observed a significant decrease in the ferroptotic mitochondria within the neuron. Reduced glutathione assay, cysteine assay, and homocysteine assay *in-vitro* model showed that Comp-23 maintained S-adenosylhomocysteine hydrolase activities against lipid peroxidation. Co-immunoprecipitation showed that this may be attributed to the preserved interaction between DJ-1 and S-adenosylhomocysteine hydrolase-like protein 1. Overall, our findings suggested that anti-DJ-1-oxidation can be a therapeutic target after ICH by reducing neuronal ferroptosis.

Disclosures: C. Zhang: None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.08/C154

Topic: C.09. Stroke

Support: NIH R01NS115759
NHLBI T35
HL120835

Department of Veterans Affairs
Stritch School of Medicine STAR program

Title: Delayed TrkA activation improved functional outcome after ischemic stroke in adult rats

Authors: *S.-Y. TSAI[1], E. GINO[2], D. NGUYEN[2], S. T. TON[1], R. NOCKELS[3], G. KARTJE[1]; [1]Res. Service, Edward Hines Jr VA Hosp., Hines, IL; [2]Stritch Sch. of Med., Loyola Univ. Chicago, Maywood, IL; [3]Neurosci., Endeavor Hlth. Northwest Community Healthcare, Arlington Heights, IL

Abstract: Stroke is a leading cause of disability in the United States and the general population worldwide. Currently there are no successful treatments to restore normal function to stroke patients once brain damage has occurred. Our laboratory has pioneered antibody therapy directed at the neurite inhibitory protein Nogo-A to promote neuroplasticity and improve post-stroke recovery. Our previous study showed that Nogo-A blocks nerve growth factor (NGF)-dependent TrkA phosphorylation and activates a ceramide-dependent pathway, which negatively influences neuronal survival and neurite outgrowth. These findings suggest that Nogo-A may interfere with the intrinsic neurotrophin-dependent plasticity that mediates recovery. Therefore, we hypothesized that direct activation of the TrkA signaling pathway after ischemic stroke would improve sensorimotor outcome and enhance neuronal plasticity. We examined the effect of a selective TrkA agonist, gambogic amide (GA) on functional recovery after middle cerebral artery occlusion (MCAO) in adult male, Long Evans, black hooded rats. Animals were first trained on the skilled forelimb reaching task and horizontal ladder walk task. The rats then received MCAO surgery on the side corresponding to the preferred limb and one week post-stroke were either treated with the TrkA agonist GA or vehicle. Behavioral testing was conducted from three days after stroke until eight weeks after treatment. At the end of behavioral tests, the anterograde neuronal tracer biotinylated dextran amide (BDA) was injected into the intact contralesional forelimb cortex to determine axonal plasticity. Behavioral results indicate that rats treated with GA showed significant improvement in functional outcome as compared to control rats ($p<0.05$, repeated measures ANOVA) with anatomical analysis to determine axonal plasticity still undergoing. Our results suggest a new strategy for enhancing functional recovery after stroke, and further support our previous study that Nogo-A is a negative regulator of neurotrophin signaling following brain injury.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.09/C155

Topic: C.09. Stroke

Support: R21NS123531

Title: Efficacy of an oxygen carrier in improving functional and anatomical outcomes after subarachnoid hemorrhage

Authors: *M. AHMED;
Henry Ford Hlth., DETROIT, MI

Abstract: Efficacy of an oxygen carrier in improving functional and anatomical outcomes after subarachnoid hemorrhage
M.E AHMED [1], N. AKHTER [1], S. FATIMA [1], S. GIRI [1], M.N. HODA [1], A.S. AHMED
[11]Department of Neurology, Henry Ford Health, Detroit, MI 48202
Background: Subarachnoid hemorrhage (SAH) is the deadliest type of stroke. Post-SAH vasospasm attenuates tissue oxygenation which subsequently leads to brain damage and functional deficits. However, translational studies focused on post-SAH brain tissue oxygenation to improve functional outcomes remain limited. We propose perfluorocarbon (PFC)-Oxygent, a lipid emulsion oxygen carrier, as a potentially effective treatment to improve post-SAH functional and anatomical outcomes. PFC-Oxygent is supplied as a highly malleable lipid emulsion of micro-particles. The ultra-smaller size of PFCs in comparison to RBCs enables them to circulate even in the presence of minimal residual plasma, thus allowing them to efficiently deliver oxygen and prevent tissue injury. We tested the hypothesis that PFC-Oxygent would attenuate SAH-mediated functional and anatomical deficits.**Methods:** Adult C57BL/6 wild-type mice were subjected to the end perforation model of SAH followed by an *i.v* injection of PFC-Oxygent or saline. Mice were tested for functional outcomes followed by blood collection via cardiac puncture at 48h after SAH. Thereafter, mice were transcardially perfused, and brains were harvested to assess different immunohistochemical and biochemical outcomes.**Results:** We found that SAH resulted in significant neurologic and motor deficits while PFC-Oxygent treatment attenuated these functional deficits. We also found that SAH-induced vasospasm, RBC deformability, and endothelial dysfunction were also restricted by PFC-Oxygent treatment. There was a significant neuronal death after SAH as compared with the sham group and PFC-Oxygent prevented neuronal death. We also found attenuation in mitochondrial fragmentation in post-SAH PFC-Oxygent treatment group when compared with the vehicle-treated SAH group.
Conclusion: These data demonstrated that PFC-Oxygent treatment maintains mitochondrial dynamics, reduces tissue damage, and improves functional outcomes. Our novel preliminary study on SAH encourages us to explore the mechanism of action of Oxygent-PFC and a comprehensive preclinical trial to test its efficacy in various animal models of SAH.

Disclosures: M. Ahmed: None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.10/C156

Topic: C.09. Stroke

Support: VA Merit Research Award I01BX002661
VA Merit Research Award I01BX006240-0
NIH RO1 grant AA028175-01
MU Research Council (URC-22-006

Title: Chemogenetic activation of melanin concentrating hormone neurons corrects sleep disturbances and promotes recovery after ischemic stroke

Authors: *A. CHISCHOLM[1], R. SHARMA[1], M. PARIKH[2], M. M. THAKKAR[3];
[1]Neurol., Univ. of Missouri, Columbia, MO; [2]Univ. of Missouri, Columbia, Columbia, MO;
[3]Neurol., HSTMV Hospital/University of Missouri, Columbia, MO

Abstract: Title: Chemogenetic activation of melanin concentrating hormone neurons corrects sleep disturbances and promotes recovery after ischemic strokeAuthors: Abigail Chischolm, MS; Rishi Sharma, PhD; Meet Parikh, MS and Mahesh M. Thakkar, PhD.**Affiliations:** Harry S. Truman Memorial Veterans Hospital and Department of Neurology, University of Missouri-School of Medicine, Columbia, MO
Background: Ischemic stroke (IS) is the fifth leading cause of mortality and the highest contributor to disability annually. The majority of stroke survivors display sleep disturbances, including insomnia and daytime sleepiness, which negatively impact recovery while accentuating the risk for stroke recurrence. These post-stroke sleep disturbances are considered a potential therapeutic target for stroke management and rehabilitation; however, the underlying mechanism of IS-induced sleep disturbances and its impact on stroke recovery is still unknown. Melanin-concentrating hormone (MCH) plays a pivotal role in the regulation of many physiological functions, including a) sleep (especially REM sleep), b) learning and memory, c) locomotor activity and energy expenditure via modulation of the activity of GABAergic neurons and dopaminergic tone in the striatum. Recently, MCH has been involved in regulating oxidative stress, neuroinflammation, and circadian genes via the SIRT-1 pathway, and its potential as an anti-stroke agent has been envisaged; however, it has never been investigated. This led to the hypothesis that ***"MCH activation will promote sleep and recovery in mice with IS."***Transgenic MCH-cre C57BL/6J mice (expressing cre recombinase in the MCH neurons) instrumented with sleep recording electrodes were used to test our hypothesis. IS was induced utilizing a widely used middle cerebral artery occlusion (MCAO) method. Designer Receptor Exclusively Activated by Designer Drug (DREADD) was employed to selectively activate MCH neurons for sleep promotion. **Results:** Mice subjected to IS displayed insomnia-like symptoms, excessive daytime sleepiness, and motor and cognitive deficits until day 7 post-IS. Chemogenetic activation of MCH on Days 1 and 2 post-IS attenuated IS-induced effects on sleep-wakefulness, sensorimotor, and cognitive behavior.**Conclusions**: Our findings strongly indicate that sleep disturbances following IS negatively impact post-stroke recovery. Additionally, MCH may serve as a novel therapeutic target for treating sleep disturbances and promoting accelerated recovery post-IS.

Disclosures: A. Chischolm: A. Employment/Salary (full or part-time):; University of Missouri, Harry S. Truman VA Hospital. **R. Sharma:** A. Employment/Salary (full or part-time):; University of Missouri, Harry S. Truman VA Hospital. **M. Parikh:** A. Employment/Salary (full

or part-time):; University of Missouri, Harry S. Truman VA Hospital. **M.M. Thakkar:** A. Employment/Salary (full or part-time):; University of Missouri, Harry S. Truman VA Hospital.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.11/C157

Topic: C.09. Stroke

Support: CONACyT A1-S-21433

Title: S-allyl cysteine (SAC) treatment increases BDNF, VEGF, and NGF expression after middle cerebral artery occlusion in different brain regions

Authors: *S. BAUTISTA PÉREZ[1], J. PEDRAZA CHAVERRI[2], J. LARA ESPINOSA[3], R. HERNANDEZ PANDO[3], A. LOREDO-JASSO[4], D. BARRERA-OVIEDO[5], C. A. SILVA-ISLAS[6], P. MALDONADO[7];
[1]Facultad de Medicina UNAM, CDMX, Mexico; [2]Univ. Nacional Autónoma de México, Mexico, Mexico; [3]Inst. Nacional de Nutrición, Mexico, Mexico; [4]Dept. de Ciencias Ambientales y del suelo, Lab. de Geoquímica Ambiental Mol., Mexico, Mexico; [5]Dept. of Pharmacol., Fac. of Med., Natl. Autonomous Univ. of Mexico, Mexico, Mexico; [6]Patología Vascular Cerebral, Inst. Nacional De Neurología Y Neurocirugía, Ciudad De México, Mexico; [7]Pharmacol., Univ. Nacional Autónoma de México, Mexico City, Mexico

Abstract: Stroke is a leading cause of disability worldwide. After a stroke, some mechanisms of repair and damage are activated in the cells. However, in some cases, the repair is not enough to reestablish the cognitive and motor dysfunction of the survivors. Neurogenesis and neuroplasticity are repair mechanisms regulated by neurotrophins and activated after stroke. Many compounds could modulate neurogenesis and neuroplasticity, such as SAC the major organosulfur compound in the aged garlic extract. After stroke, SAC diminishes the damage, but the neurotrophic effect has not been studied. The aim is to know if SAC treatment affects neurotrophins expression. Female rats were divided into 4 groups: Control, SAC, IR, and IR+SAC. Animals of the control group were subjected to surgery process without the middle cerebral occlusion. Animals of IR and IR+SAC groups were subjected to middle cerebral artery occlusion. SAC group was treated with SAC for 15 days. The treatment of IR+SAC was the same but started at the reperfusion onset. Control and IR groups were administered with an isotonic solution. As was observed previously animals subjected to IR and treated with SAC have minor motor deficit scores and histology damage, 15 days after reperfusion onset. BDNF expression increased in animals of SAC group. VEGF expression increased in the striatum of IR+SAC group. NGF expression increased in the cortex of IR+SAC group. Finally, SAC treatment did not modulate the expression of NT4. In conclusion, SAC could modulate the neurotrophins expression, directly or indirectly, increasing the repair mechanisms. This work was partially supported by project A1-S-21433, CONACYT (PDM).

Disclosures: **S. Bautista Pérez:** None. **J. Pedraza Chaverri:** None. **J. Lara Espinosa:** None. **R. Hernandez pando:** None. **A. Loredo-Jasso:** None. **D. Barrera-Oviedo:** None. **C.A. Silva-Islas:** None. **P. Maldonado:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.12/C158

Topic: C.09. Stroke

Support: American Heart Association (AIREA grant #957277)
College of Medicine, Central Michigan University

Title: Crispr/cas9 mediated genes knockout in primary adult rat astrocytes for neuronal reprogramming

Authors: *A. POUDEL[1,3,4,5], B. SRINAGESHWAR[1,5,3], S. SCHWIND[1,3,2,4], E. A. NISPER[1,5], L. BOLEN[1,3,2,4], A. UPRETY[1,3,2,4], N. DAY[1,3,6], A. SHARMA[1,6], G. L. DUNBAR[1,2,3,4], J. BAKKE[1,5], J. ROSSIGNOL[1,5,3,4];
[2]Psychology, [1]Central Michigan Univ., Mount Pleasant, MI; [3]Field Neurosciences Inst. Lab. for Restorative Neurol., Mount Pleasant, MI; [4]Program in Neurosci., Mount Pleasant, MI; [5]Col. of Med., Mount Pleasant, MI; [6]Dept. of Chem. & Biochem., Mount Pleasant, MI

Abstract: Hypoxic injury leads to neuroinflammation, causing neuronal death, which triggers an immune response that activates the protective functions of astrocytes, also known as reactive astrocytes. Previous research has shown that it is possible to convert these astrocytes into functional neurons by inhibiting specific pathways, including the Notch, GSK-3 β, and BMP pathways. In this study, we used the CRISPR/Cas9 gene-editing tool to knock out the target receptor-associated genes *Psen1* for Notch pathways, *Bmpr1a* for BMP pathway, and *Gsk3b* for GSK-3β in adult rat brain-derived astrocytes. Sanger sequencing showed knockout of the above-mentioned genes. We performed immunocytochemistry in *Psen*1, *Gsk3b*, and *Bmpr1a* treated primary rat astrocytes and observed the expression of neuronal marker Tuj1 after 28 days of transfection. Western blot analysis showed an alteration in the expression of the target proteins of each pathway in HEK T293 cells, which were used as control, suggesting the successful knockout of the above-mentioned target genes. This study aimed to investigate potentially using G4 PAMAM dendrimers to deliver CRISPR/Cas9 to astrocytes in primary rat cell culture, as well as in an MCAo rat model, to edit the genes involved in the pathways described above to convert reactive astrocytes into neuroblasts. This preliminary study suggests that using CRISPR/Cas9 to edit genes and pathways to convert astrocytes into neurons in stroke could be a promising strategy for these therapeutics in the brain.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.13/C159

Topic: C.09. Stroke

Support: NIH Grant R01NS069726
NIH Grant R01NS0945639
AHA Grant 16GRNT31280014

Title: The effect & mechanism of GDNF released from reactive astrocytes on neuronal and brain protection after ischemic stroke

Authors: *Z. ZHANG[1,2], S. DING[3,2];
[1]Univ. of Missouri-Columbia, COLUMBIA, MO; [2]Dalton Cardiovascular Research Center, Columbia, MO; [3]Dept. of Biomed., Biol. and Chem. Engin., Univ. of Missouri, Columbia, MO

Abstract: Focal ischemic stroke (FIS) is a serious neurological disease. Astrocytes are the predominant glia cell types in the central nervous system (CNS) and undergo transformation to a reactive state after FIS. This process is termed reactive astrogliosis and the activated cells are called reactive astrocytes. Reactive astrogliosis is a hallmark of FIS and contributes to tissue remodeling and functional recovery following FIS. Glial cell-derived neurotrophic factor (GDNF) was originally isolated from a rat glioma cell-line supernatant and has been discovered to be a potent survival neurotrophic factor for dopaminergic, noradrenergic and motor neurons. In our previous study, we found that deletion of GDNF in astrocyte leaded to increased neuronal death and brain damage after photothrombosis (PT)-induced FIS. Moreover, GDNF deletion inhibited reactive astrogliosis, suggesting astrocyte derived GDNF can promote neural survival. Here, we tested whether overexpression of GDNF in astrocytes had neuronal and brain protective effect after ischemia. First, we constructed AAV vectors with astrocyte-promotor to overexpress GDNF in astrocytes. We observed that astrocyte specific GDNF overexpression decreased brain infarction and promoted motor function recovery after PT. We also found that overexpression of GDNF promoted reactive astrogliosis and reduced oxidative stress in the peri-infarct region (PIR) after ischemic stroke. Second, to test whether it is extracellular GDNF released from astrocytes exert its neuronal and brain protective effect after ischemia, we cultured primary astrocytes and transfected with DNA plasmid encoding GDNF. Using ELISA, we found GDNF concentration was significantly elevated in astrocyte medium after oxygen-glucose deprivation (OGD), and GDNF concentration was further elevated in medium after DNA transfection. Moreover, astrocyte condition medium (ACM), collected from OGD subjected astrocyte culture, significantly increased neuronal survival after OGD while GDNF neutralizing antibody suppressed this beneficial effect. Lastly, we found that astrocyte derived GDNF triggered the activation of Ret receptor in cultured neurons and suppressed caspase-dependent cell apoptosis after OGD. Collectively, our study underscores the importance of reactive astrocytes in neuronal

and brain protection after ischemia and suggests that promoting endogenous neurotrophic factor release from reactive astrocytes might be a potential approach in stroke therapy.

Disclosures: Z. Zhang: None. **S. Ding:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.14/C160

Topic: C.09. Stroke

Support: URI^2 Undergraduate Research Grant

Title: Exploring the neuroprotective effects of phytocannabinoids on oxygen-glucose deprived neurons in an in-vitro model of stroke

Authors: *B. CHATRAGADDA[1,2,3], E. POTTS[4], H. MA[5], N. SEERAM[4,6], C. FALLINI[7,3,6]; [1]Univ. of Rhode Island, Kingston, RI; [2]Cell and Molecular Biology, University of Rhode Island Interdisciplinary Neuroscience Program, Kingston, RI; [3]University of Rhode Island Interdisciplinary Neuroscience Program, Kingston, RI; [4]Univ. of Rhode Island Interdisciplinary Neurosci. Program, Kingston, RI; [5]Univ. of Rhode Island Col. of Pharm., Kingston, RI; [6]University of Rhode Island College of Pharmacy, Kingston, RI; [7]Cell and Mol. Biol., Univ. of Rhode Island Interdisciplinary Neurosci. Program, Kingston, RI

Abstract: Stroke is a leading cause of long-term disability and decreased mobility worldwide. During stroke, neuronal damage results from both the initial oxygen-glucose deprivation and the increase in excitotoxicity and oxidative stress after restoration of blood flow, a phase called Ischemia-Reperfusion Injury (IRI). Reducing the negative impact of IRI on neuronal health could result in better outcomes for post-stroke patients by preventing excessive neuronal death. Although it has been reported that phytocannabinoids may exert neuroprotective against ischemic stroke by modulating glial cells, their mechanisms of action are not well studied. We thus hypothesized that treating neurons exposed to an acute ischemic event with phytocannabinoids could lead to reduced toxicity and overall promote improved viability. To test this hypothesis, we have optimized an in vitro stroke platform using iPSC-derived human cortical neurons that allows the screening of multiple compounds simultaneously in a medium-throughput format. We show that our imaging and analysis protocol can accurately quantify rates of neuronal death in an automated manner using standard ImageJ-based tools. Our results suggest that the effects of IRI can be observed up to seven days after the acute ischemic event and neurons treated with a panel of phytocannabinoids including cannabidiol and minor cannabinoids had reduced rates of cell death compared to untreated controls. These findings could provide evidence that phytocannabinoids may serve as therapeutics to prevent neuronal death in post-stroke patients.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.15/D1

Topic: C.09. Stroke

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National Institutes of Health (NINDS-NS-052727)
National Institute on Aging, Award Number T32AG061897, KB
and Achievement Rewards for College Scientists (ARCS), KB

Title: Pituitary Adenylate Cyclase-Activating Polypeptide glycosides promote cell outgrowth in vitro and reduce infarct size after stroke in a preclinical model

Authors: K. BERNARD[1], M. L. HEIEN[2], R. POLT[3], H. MORRISON[4], *T. FALK[5];
[1]Neurol., Univ. of Arizona, Tucson, AZ; [2]Chem. and Biochem., Univ. of Arizona, Tucson, AZ; [3]Chem. & Biochem., The Univ. of Arizona, Tucson, AZ; [4]Col. of Nursing, Univ. of Arizona, Tucson, AZ; [5]Univ. of Arizona, Tucson, AZ

Abstract: Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) is an endogenously expressed peptide that has been shown to act in a multi-modal fashion and promote processes such as modulation of inflammation and reduction of excitotoxic damage, that could be beneficial in the context of neural damage and cell death after stroke. However, despite PACAP's neurotrophic and anti-inflammatory properties, it has not realized its translational potential as a result of poor stability (short duration of half-life) and limited Blood-Brain Barrier Penetration (BBB) permeability. We have previously shown that glycosylation of PACAP results in improved drug lifespan and BBB penetration after systemic injection. In addition, our prior work proved reduced neuronal cell death and modulation of neuroinflammation in models of Parkinson's disease and Traumatic Brain Injury (TBI) after systemic treatment. In the present study we show that a $PACAP_{(1-27)}$ glucoside retains the known neurotrophic activity of native $PACAP_{(1-27)}$ *in vitro* and after 5 days of treatment (100 nM) results in differentiation in PC12 cells; a decreased number of cells per frame relative to the vehicle group, an increase in cell diameter and development of neurite-like extensions in the PC12 cells. The effect size of both the glycoside and the native PACAP were almost identical. In addition, we show that systemic injection (intraperitoneal) of a $PACAP_{(1-27)}$ lactoside (10 mg/kg) with improved BBB-penetration, when given 1-hour after reperfusion in a Transient Middle Cerebral Artery Occlusion (tMCAO) mouse model, reduces the infarct size after the ischemic injury in male mice significantly by ~36% ($p < 0.05$, one-way ANOVA, Šidák's test of multiple comparisons). At a 1 mg/kg dose a smaller effect size is seen, ~26% reduction of infarct size, indicating a possible dose-dependency. In conclusion, our data support further preclinical development of PACAP

glycopeptides as promising novel drug candidates for the treatment of stroke, an area with a tremendous clinical need for new therapeutics.

Disclosures: **K. Bernard:** None. **M.L. Heien:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MLH holds patents related to the content and has equity in Teleport Pharmaceuticals, LLC, a UArizona biotech startup. **R. Polt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RP holds patents related to the content and has equity in Teleport Pharmaceuticals, LLC, a UArizona biotech startup.. **H. Morrison:** None. **T. Falk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TF holds patents related to the content and has equity in Teleport Pharmaceuticals, LLC, a UArizona biotech startup..

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.16/D2

Topic: C.09. Stroke

Support: Allen and Company
Stein Family Research Fund
Marcus Foundation

Title: Progesterone Attenuates Diabetic Stroke-Induced Brain Damage via Inhibition of Endoplasmic Reticulum Stress

Authors: *S. YOUSUF[1], D. G. STEIN[2], F. ATIF[3];
[1]Radiation Oncology, Emory Univ., Atlanta, GA; [2]Emergercy Med., Emory Univ., Atlanta, GA; [3]Emergency Med., Emory Univ., Atlanta, GA

Abstract: Objective: We investigated whether progesterone treatment (P4) modulates endoplasmic stress (ER) and behavioral outcomes in a transient middle cerebral artery occlusion (tMCAO) model of stroke in rats with Type II Diabetic (DM) condition. **Method:** Type 2 diabetes (DM) was induced in young male Wistar rats by a single injection (*i.p*) of streptozotocin and nicotinamide. The animals were kept in diabetic conditions for 6 months to mimic the chronic effects of diabetic pathology in human patient population. The rats were assigned to 4 groups: Sham, tMCAO, tMCAO+DM, and tMCAO+DM+P. After 6 months, tMCAO was induced and P4 was administered (*s.c*) 1h post-occlusion, then daily for 3 days. Behavioral testing (tail flick, hot-plate, locomotor, somatosensory neglect and grip strength) was done on day 4 post-stroke. After evaluating the behavioral outcomes post stroke, brains were harvested for immunostaining and Western blot analysis. **Results:** The tMCAO groups showed a significant *($p<0.05$)* impairment in all behavioral outcomes as compared to the sham group. The

behavioral outcomes were severely impaired ($p<0.05$) in the tMCAO+DM than the tMCAO group. The P4 treated group showed improved *($p<0.05$)* behavioral outcomes as compared to the tMCAO and tMCAO+DM groups. Diabetic stroke significantly increased ($p<0.05$) the neuroinflammatory response as evidenced by expression of GFAP and Iba-1 in ischemic animals compared to controls; increased inflammatory response was seen (*$p<0.05$*) more significant in the tMCAO+DM group compared to the tMCAO group. A significant *($p<0.05$)* decrease was seen in tMCAO+DM+P group as compared with the tMCAO and tMCAO+DM groups. In tandem, enhancement of hippocampal ER stress was evidenced by the activation of PERK/CHOP axis seen by increased protein expression of PERK, and CHOP signal proteins in the hippocampi of tMCAO and tMCAO+DM groups. Interestingly, progesterone treatment modulated the ER stress in tMCAO+DM+P4 group significantly as compared with the tMCAO and tMCAO+DM groups. **Conclusion:** The current results suggest the promising neuroprotective actions of progesterone treatment in diabetic stroke by dampening inflammation, ER stress, and the associated PERK/CHOP pathway with improved behavioral outcomes.

Disclosures: S. Yousuf: None. **D.G. Stein:** None. **F. Atif:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.17/D3

Topic: C.09. Stroke

Support: NIH Grant R01NS104117
NIH Grant R01NS109221
CIHR Grant DFSA-187707

Title: Single-cell multiome analysis reveals elovanoids protection by selective modulation of neuronal and glial phenotypes in experimental ischemic stroke

Authors: *J. JI, S. BHATTACHARJEE, L. BELAYEV, N. G. BAZAN;
LSU Hlth. New Orleans, New Orleans, LA

Abstract: Ischemic stroke is a leading cause of death and disability in the world, and a large proportion of survivors display the onset of cognitive impairments. Currently, the only available pharmacological therapy after stroke is tissue plasminogen activator which restores blood flow but do not combat the inflammatory aftermaths of ischemia-reperfusion injury. Administration of a novel class of very long-chain polyunsaturated fatty acids (VLC-PUFAs) derivatives termed elovanoids (ELV34) or its VLC-PUFA precursor (FA34) has shown protective effects in both in vitro and in vivo models of uncompensated oxidative stress and ischemic stress. We found that ELV34 or FA34 delivery attenuates sensorimotor deficits after ischemic stroke. Furthermore, we uncovered that ELV and its precursors protect against ischemic damage by altering the phenotype of glial cells and modulating the expression of pro/anti-inflammatory and

neuroprotective genes. We used 10X Single Cell Multiome (ATAC + Gene Expression) to compare genomic and epigenomic responses in naïve rats and after experimental ischemic treatment. Adult Sprague-Dawley rats underwent 2 hours of middle cerebral artery occlusion (MCAo) via intraluminal suture. Rats received vehicle, ELV34, or FA34 delivered intranasally 1 hour, 1 day, and 2 days after 2 hours of MCAo. Neurological scoring consisting of postural reflex and forelimb placement tests and various physiological measures were collected. Brains were harvested on day 3 from the ipsilesional cortex (penumbra region) and subcortex. Nuclei were isolated and processed according to 10X Genomics Single Cell Multiome protocol. ELV34 or FA34 treatment both reduced neurological deficits after MCAo. Joint RNA + ATAC single-cell analysis revealed an increase in microglia and leukocyte abundance as well as a loss of neuronal populations after MCAo. ELV34 or FA34 reduced the loss of neuronal populations and restored the pool of homeostatic microglia after stroke. Furthermore, differential gene expression analysis revealed that ELV or its precursor regulated pathways related to phagocytic clearance, inflammatory signaling, and cellular trafficking to promote neuroregeneration in microglia, astrocytes, neurons, and other neural cells. In summary, ELV/precursors may exert their bioactivity by modulating conversion to neuroprotective cell phenotypes in neurodegenerative diseases such as stroke, traumatic brain injury, or Alzheimer's disease.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.18/Web Only

Topic: C.09. Stroke

Title: A small molecule TrkB receptor agonist reduces thalamic damage following cortical ischemic stroke

Authors: I. PARADA[1], T. YANG[1], A. DELGADO[2,3], F. M. LONGO[1], D. A. PRINCE[1], ***F. GU**[2];
[1]Neurol., Stanford Univ. Sch. of Med., Palo Alto, CA; [3]Biol. Sci., [2]Univ. of North Texas, Denton, TX

Abstract: After cortical ischemic stroke, in addition to direct neocortical damage induced by a focal infarction, there is a cascade of neuroinflammation and secondary neuronal damage occurring over time in the thalamus. This contributes significantly to chronic post-stroke outcomes. Understanding the mechanisms underlying the development of the chronic secondary thalamic damage is crucial for devising effective strategies to prevent or treat long-term disability following cortical stroke. Studies have demonstrated that activation of microglia contributes to inflammation-related neuronal damage through its release of cytokines, leading to the formation of neurotoxic A1 astrocytes, which drive neuronal death. These findings led us to hypothesize that microglia activation in thalamus following cortical stroke triggers the formation

of A1 astrocytes, ultimately leading to secondary neuronal damage in the thalamus. To test this hypothesis, we conducted immunohistochemical experiments in a rat model of cortical photothrombotic stroke and observed significant neuron loss in thalamic nRT, VPL, and VPM nuclei 8 days after cortical stroke. The neuronal loss was accompanied by microgliosis, astrogliosis, reactive neurotoxic A1 astrocytes, and upregulated c1q, IL-1α, TNFα, suggesting that neurotoxic A1 astrocytes may contribute to the secondary neuronal damage in the thalamus. Furthermore, given that BDNF-TrkB signaling has been shown to inhibit microglial activation by previous studies, we investigated whether a small molecule TrkB-receptor partial agonist PTX BD4-3 (BD) can rescue the post-stroke thalamic damage by inhibiting microglia activation and A1 astrocyte formation. To test this hypothesis, BD was administered intraperitoneally for 7 days immediately after stroke induction. Two days after the last treatment, animals were perfused for immunohistochemistry. Results indicated that BD treatment decreased microgliosis, the levels of c1q, IL-1α, and TNFα, number of neurotoxic A1 astrocytes, as well as neuron loss in the affected thalamic regions. In summary, our findings suggest that systemic partial TrkB receptor agonist treatment could be a potential strategy to reduce neuroinflammation and neuronal damage in the thalamus after cortical stroke.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.19/D4

Topic: C.09. Stroke

Support: CIHR

Title: Transplantation of human directly reprogrammed neural precursor cells to treat chronic stroke

Authors: K. GILMORE, C. MORSHEAD;
Surgery, Univ. of Toronto, Toronto, ON, Canada

Abstract: Background: Stroke is a leading cause of acquired long-term disability worldwide. There are 15 million new cases of stroke each year and currently 5 million patients living with chronic disabilities. There are limited interventions to treat the stroke injured brain and no treatments to improve the chronic condition. Chronic stroke is understudied. We sought to determine whether a population of human directly reprogrammed neural precursor cells (drNPCs), previously shown to improve cellular and behavioural outcomes in the sub-acute phase post-stroke, are efficacious in a model of chronic stroke. We **hypothesize** that drNPCs will enhance neuroplasticity and support improved functional outcomes. **Methods:** We established a photothrombic model of sensory-motor cortical stroke in immunocompromised (SCID-Beige)

mice that results in long-term motor impairments (up to 3 months post-stroke). Mice received stroke+vehicle (aCSF) or stroke+drNPCs (~150,000 cells transplanted directly into the stroke injury site at 3 weeks post-stroke). We performed behavioural assays (grip strength and horizontal ladder) pre-stroke (baseline), 20 days post-stroke (prior to cell transplantation) and up to 60 days post-drNPC transplant. Mice were sacrificed at various times post-transplantation and the number, location and differentiation profile of transplanted cells was examined. **Results**: Mice that received drNPC transplants had significantly improved motor function compared to stroke+vehicle treated mice as early as 28 days post-transplantation, and the improvement was maintained until sacrifice. Transplanted cells were identified in the stroke injury site using Human Nuclear Antigen (HuNu) and at 14 days post-transplant (a time when functional recovery is not observed), the majority of the $HuNu^+$ cells expressed glial fibrillary acidic protein (GFAP), a marker of neural stem cells and astrocytes. **Conclusion:** We find that drNPC transplantation in the chronic phase post-stroke leads to improved functional recovery, arguably the most clinically relevant measure of success. Determining the cellular correlates that underlie the functional outcomes affords an understanding of novel therapeutic targets for future interventions.

Disclosures: K. Gilmore: None. **C. Morshead:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.20/D5

Topic: C.09. Stroke

Support: Thematic Funding from Ministry of Education and Science of Armenia (PI: Kristine Danielyan; N 21T-1F174)

Title: Creation of PEG/albumin carriers loaded with medicines for the treatment of experimental stroke

Authors: *K. DANIELYAN[1,2], V. ATOYAN[1], A. TSOKOLAKYAN[3], N. ZAQARYAN[1], A. AL-ISAWI[4], S. CHAILYAN[1];
[1]H. Buniatian Inst. of Biochem., Yerevan, Armenia; [2]Eurasia International University, Yerevan, Armenia; [3]A. B. Nalbandyan Inst. of Chemical-Physics, Yerevan, Armenia; [4]Eurasia Intl. Univ., Yerevan, Armenia

Abstract: Background. The high incidence of stroke in low- and middle-income countries is caused by a number of factors, such as undiagnosed and untreated hypertension, a lack of easily accessible high-quality health services, air pollution, unhealthy lifestyles (such as poor diet, smoking, sedentary behavior, and obesity) etc. One of the advanced directions in Pharmacology is the “Targeted Drug Delivery”. One of the tools of mentioned direction is the utility of the drug carriers. Due to the efficient delivery of the medicines, the side effects of medicines are profoundly diminished. We aimed to investigate thoroughly physical-chemical characteristics of

the carriers, bearing the stroke treating medicines: dexamethasone, allopurinol, PRP-1 (native Proline Rich Peptide-1), coated and covered with PEG in the setting of experimental stroke in rats. **Methods.** The particles were prepared with the utility of the PRP-1 (neuroprotector), dexamethasone (to depress the inflammation after the stroke), allopurinol (suppressor of the free radicals' syntheses). The hydrodynamic diameters of the particles were obtained with dynamic light scatterer by using a Litesizer™ 500 (Anton Paar, Graz, Austria). The ζ-potential was determined using Omega cuvette Z (Anton Paar) at 25°C, applying a 40 mW and 658 nm wavelength laser. Stability of the particles was checked by HPLC. The oxidative damage of the stroke development phase was induced by the injection of hydrogen peroxide into the temporal part of the cortex: 2 mm lateral to midline, 3 mm anterior, 2 mm below the surface of the skull. **Results.** Prepared albumin nanoparticles had the diameter 22.61 nm (63.74 %) and 468.27 nm in average (36.26 %). The diameter of the loaded with the medicines PEG/particles was 164.098 nm (98.89 %) and 3119.61 nm (1.11 %). ζ-potential of the PEG/albumin/medicines particles was the lowest -18. The circulation of the PEG/albumin/medicines parties was the longest: at day 7th it reached 50% of the initial dose in comparison with the albumin particles (0 %). PEG/albumin/medicines particles remained stable up to 1 month. Results regarding preservation of BBB (Blood Brain Barrier) in stroke model were not statistically significant for chosen time and dosage of the treatment. **Conclusions:** Stable, small (predominant percentile of the particles was 200 nm) long lasting in blood stream drug-carriers were created. The further in vivo experiments with the utility of the stroke models are required.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.21/D6

Topic: C.09. Stroke

Support: QPG-327008-NUTTIN-FWO-SBO-SCATMAN
EFD-LSMDT5-O2010

Title: Subthalamic and cortical delta and gamma oscillations pathologically decrease in rats with acute stroke

Authors: *Z. DENG[1], U. KILIC[1], M. MC LAUGHLIN[2], B. NUTTIN[1,3];
[1]Dept. of Neurosciences, [2]Neurosci., KU Leuven, Leuven, Belgium; [3]UZ Leuven, Leuven, Belgium

Abstract: Background: Recent studies have underscored the significance of delta and gamma oscillatory activities during motor execution. However, the effects of acute stroke on delta and gamma oscillations in peri-infarct and infarct regions, as well as the subthalamic nucleus (STN),

remain unclear. **Objective**: To explore the effects of acute stroke on delta and gamma oscillations in STN and motor cortex in rats with acute stroke**Methods**: Sprague-Dawley rats weighing 290-350g were included in this study. A photothrombotic ischemic lesion was induced in the motor cortex at the following coordinates: 0.5 mm posterior, 4.5 mm anterior and 3 to 4 mm lateral to bregma. The STN ipsilateral to the stroke lesion site (n=12), as well as the peri-infarct and infarct regions (n=13), were simultaneously recorded before and within 30 minutes after stroke. The recording in peri-infarct region was 2mm lateral to bregma and 2.52mm anterior to bregma, 1mm below the dura. The recording in infarct region was 3.4 mm lateral to bregma and 2.52mm anterior to bregma, 1mm below the dura. H&E stain was applied to confirm the position of electrode. 2,3,5-Triphenyltetrazolium chloride (TTC) staining was used to confirm the stroke lesion was successfully created in motor cortex. **Results**: Wilcoxon signed rank test was used for the statistical analysis. After a stroke, both delta and gamma mean power, as well as the delta peak power, were significantly
reduced in STN (p<0.05). The spike rate declined significantly from 61 spikes per second (spk/s) to 14 spk/s (p<0.05). In the infarct region, the delta mean power and delta peak power were significantly reduced after stroke (p<0.05), while they remained unchanged in peri-infarct region. Additionally, the delta and gamma mean power, as well as the peak power, were significantly reduced in both the infarct and peri-infarct regions following the stroke (p<0.05). The stroke lesion was successfully created in the motor cortex, as evidenced by the TTC staining. Additionally, the electrode was precisely implanted in STN, as confirmed by the H&E staining.**Conclusions**: The pathological reduction of delta and gamma oscillations observed in STN and motor cortex may play a role in acute stroke.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

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Program #/Poster #: PSTR020.22/D7

Topic: C.08. Ischemia

Support: CIHR 60-28350-10028283-00000 "Pannexin 1 opening in neurons"
CIHR 60-20350-10028284-00000 "Mechanism of suppression of excitotoxicity by amyloid-beta"

Title: Induction and monitoring of focal stroke in freely behaving mice reveals sex differences in spreading depolarization and associated behavior

Authors: *A. K. J. BOYCE[1], Y. FOUAD[2], R. C. GOM[3], L. A. MOLINA[2], C. M. SILVA[4], C. ENS[2], T. FUZESI[2], G. TESKEY[3], R. J. THOMPSON[5];
[1]Cell Biol. & Anat., Hotchkiss Brain Inst., Univ. of Calgary, Calgary, AB, Canada; [2]Univ. of Calgary, Calgary, AB, Canada; [3]Cell Biol. & Anat., Univ. of Calgary, Calgary, AB, Canada; [4]UFMG, Belo Horizonte, Brazil; [5]Hotchkiss Brain Inst., Univ. of Calgary, Calgary, AB, Canada

Abstract: Stroke is a leading cause of death and disability across the globe, causing significant strain on those affected, their caregivers, and healthcare systems. During ischemic stroke, an obstructed cerebral blood vessel causes focal metabolic failure and eventual necrosis in brain tissue fed by the occluded vessel. Large depolarizing and slowly propagating waves, spreading depolarizations (SD), emanate from this ischemic core to adjacent hypoperfused tissue (penumbra) and into remote healthy tissue. In penumbra, SD triggers breakdown of ionic gradients, increasing metabolic demand, challenging already vulnerable tissue, and expanding the core in the hours following stroke onset. While deleterious in penumbra, there is emerging evidence that SD is benign or even beneficial in healthy tissue. Understanding the balance between the deleterious and potentially beneficial effects of SD following stroke could vastly improve outcomes for individuals impacted by stroke. We created an all-optical method for inducing and monitoring stroke and SD in freely behaving mice, using photothrombosis to evoke unilateral stroke and fibre photometry in Thy1-GCaMP6f mice to record neuronal Ca^{2+} dynamics via bilateral fibreoptic implants. During unilateral hippocampal stroke, ipsilesional Ca^{2+} influx was similar across sexes, yet females had larger, more frequent contralesional SD, coincident with increased environmental exploration. Hippocampal stroke generated retrograde amnesia, but when contralesional SD occurred during stroke, mice had improved functional recovery and reduced anterograde amnesia. In paired local field potential recordings, epileptiform activity always preceded SD in the contralesional hippocampus. In a follow-up experiment, when SD was pharmacologically disrupted, seizures persisted and generalized, worsening outcomes. It may be the case that contralesional SD acts as an antiseizure mechanism post-stroke.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.23/D8

Topic: C.08. Ischemia

Support: AHA Grant https://doi.org/10.58275/AHA.24POST1177466.pc.gr.190941

Title: Role of TMEM97 in neuronal post-ischemic lipid homeostasis: Implications for stroke pathophysiology and therapeutic strategies

Authors: *K. ARKELIUS[1], L. GUPTA[2], M. ZHANG[1], S. WON[3], R. A. SWANSON[4], N. SINGHAL[5];
[1]UCSF, San Francisco, CA; [2]Univ. of California, Berkeley, Berkley, CA; [3]Neurol., VAMCSF & UCSF, San Francisco, CA; [4]Neurol., U.C.S.F., sausalito, CA; [5]Neurol., Univ. of California San Francisco Neurosci. Grad. Program, San Francsico, CA

Abstract: Ischemic stroke presents a significant socioeconomic burden, necessitating the exploration of innovative therapeutic avenues owing to the limited efficacy of current pharmaceutical interventions. Recent research on neurodegenerative diseases has illuminated a pathophysiological cascade characterized by abnormal lipid accumulation within glial cells, which correlates with adverse outcomes. The endoplasmic reticulum transmembrane protein 97 (TMEM97) has emerged as a promising therapeutic target due to its critical involvement in cholesterol metabolism. However, the specific role of TMEM97 in post-stroke lipid regulation remains elusive.This study aims to elucidate the impact of TMEM97 on lipid metabolism following ischemia. Initial findings demonstrate TMEM97 expression predominantly within neurons rather than astrocytes or microglia in vivo; in the mouse model, 95% of TMEM97+ cells were NeuN+ cells. In an in vitro model of lipid starvation in mouse neural progenitor cells, pharmacological inhibition of liposomal lipid release increased TMEM97 expression. Thapsigargin-induced endoplasmic reticulum (ER) stress also modulated TMEM97 expression and led to elevated low-density lipoprotein (LDL) uptake and mRNA levels of the LDL receptor (LDLR) (95% CI of 2-ΔΔCq: Control 0.9687-1.056, Thapsigargin 1.228-1.496). Spatial transcriptomic analyses following experimental stroke induction in mice revealed neuronal upregulation of crucial genes involved in lipid metabolism pathways, including LDLR, acetyl-CoA acetyltransferase 2, and peroxisome proliferator-activated receptor delta, indicating dynamic adaptations post-stroke or under cellular stressors.The observed elevation of neuronal LDLR expression in vivo closely aligns with the heightened expression of LDLR in vitro, suggesting a coordinated modulation of lipid metabolism pathways triggered by ER stress in response to stroke or metabolic stress induction. This synchronous upregulation of LDLR underscores the crucial role of ER stress as a potential trigger for this regulatory response. Additionally, considering the known involvement of TMEM97 in lipid homeostasis within the ER, it further highlights the intricate interplay between these proteins in post-stroke lipid metabolism regulation.Our findings provide a compelling starting point for further exploration into the significance of TMEM97 in post-ischemic lipid homeostasis, thereby advancing our understanding of stroke pathophysiology.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.24/D9

Topic: C.09. Stroke

Support: R01NS119319

Title: Quantitative assessments of reaching after focal ischaemic lesions in non-human primates

Authors: *A. BAINES[1], S. N. BAKER[2], J. W. KRAKAUER[3];
[1]Biosci. Inst., Newcastle Univ., Gateshead, United Kingdom; [2]Newcastle Univ., Newcastle upon Tyne, United Kingdom; [3]Neurol., Johns Hopkins Univ., Baltimore, MD

Abstract: After a middle cerebral artery stroke, damage to the motor cortex and its descending outputs causes the distinctive hemiparetic phenotype. Survivors then transition through a stereotyped sequence of recovery. Initial weakness and loss of dexterity (negative motor signs) are replaced with spasticity and abnormal muscle coactivation patterns called 'synergies' (positive motor signs). It is unknown whether damage to individual portions of the primary motor cortex (M1) hinders recovery of different components of healthy movement after stroke (strength vs control), however we know from previous mapping studies that different cortical areas possess dissimilar proportions of cortico-motoneuronal vs cortico-reticular connections. Our aim was to dissociate quantitatively the relative contributions of different divisions of M1 to the various motor deficits seen after stroke, and how this is changed after combined lesions of the magnocellular red nucleus (RNm) in monkey. 8 female rhesus macaques were trained on a reach and grasp task between a handle and a baited cup. Handle and cup positions were reconfigured so the monkey performed both flexion and extension reaches. Once fully trained, high speed videos were recorded from 3 cameras placed around the task. High speed videos were analysed using DeepLabCut and Anipose for markerless tracking of the hand in both 2D and 3D. After baseline recording, ischaemic lesions were made in the upper limb representations in anterior (n=2) and posterior (n=2) subdivisions of 'Old' M1, and 'New' M1 (n=2). These areas were defined according to differences in their cortico-motoneuronal and cortico-reticular connections. Additional animals (n=2) also received electrolytic RNm lesions before cortical lesions (anterior Old M1, n=1; entire Old M1, n=1). Hand kinematics were analysed over 15 weeks after each cortical lesion. Our results show that unlike human stroke survivors, none of the macaques developed positive motor signs post-stroke; only negative signs ensued. This is evidence that positive motor signs after stroke may result from larger cortical lesions, rather than loss of a specific M1 subdivision. We did identify quantitative differences in our reaching assessments, dependant on the lesion area and whether the animal had a RNm lesion beforehand. We also observed that deficits to movement smoothness (an analogue of proximal arm dexterity) recovered only during a recovery window of approximately 6 weeks post-lesion in all animals, no matter the severity. Conversely, movement speed continued to recover for many weeks after this acute period. Finally, we have shown that RNm damage does worsen recovery after M1 loss in monkey.

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Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

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NINDS (K23NS121628) to Aaron M. Gusdon

Title: Behavioral Profiling of Mouse Models for Stroke and Subarachnoid Hemorrhage

Authors: *S. TABASSUM[1], H. HU[2], S. WU[3], A. GUSDON[4], H. CHOI[4], X. S. REN[2];
[1]The Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [2]Neurosurg., Univ. of Texas Hlth. Sci. Ctr., Houston, Houston, TX; [3]Univ. of Texas Hlth. Sci. Ctr., Houston, Houston, TX; [4]UTHealth Houston, Houston, TX

Abstract: Behavioral Profiling of Mouse Models for Stroke and Subarachnoid HemorrhageSidra Tabassum[1], Heng Hu[1], Silin Wu[1], Aaron W. Gusdon[1], HuiMahn A. Choi[1], Xuefang S. Ren[1].1 Department of Neurosurgery, McGovern Medicine School, University of Texas Health Science Center at Houston, Houston, TX, United States.
Abstract: Brain diseases encompass a diverse array of conditions that profoundly impact cognitive, motor, and sensory functions. Among these, stroke stands as a leading cause of global disability and mortality, posing significant challenges to healthcare systems worldwide. The transient middle cerebral artery occlusion (tMCAO) model has long been a cornerstone in stroke research due to its ability to mimic human pathology effectively. However, the photothrombotic stroke (PTS) model is emerging as a promising alternative, offering simplified surgical protocols and reproducible damage. Similarly, subarachnoid hemorrhage (SAH) presents a devastating form of stroke characterized by bleeding into the subarachnoid space. Given the substantial healthcare burden posed by both stroke and SAH, ongoing research endeavors aim to unravel their underlying mechanisms and develop novel therapeutic strategies. In this study, we conducted a comprehensive assessment of behavioral outcomes in mice subjected to three distinct stroke models: tMCAO, PTS, and SAH. Utilizing a battery of behavioral assays, including the rotarod for motor function, novel object recognition test for recognition memory, Barnes maze test for spatial memory, Y-maze test for working memory, tail-suspension and sucrose preference test for depression-like behavior, open field for locomotor activity, and anxiety-like behavior, we observed significant deficits in motor function, memory, and depression-like behavior in both the tMCAO and SAH models. However, mice subjected to the PTS model exhibited impairments solely in motor function and memory, without discernible depression-like behavior. Given the established association between over-activation of the amygdala and anxiety and depression, we posited that the PTS model may not exert significant effects on deep brain structures such as the amygdala. These findings shed light on the selection of appropriate animal models for studying specific aspects of stroke pathology and associated behavioral phenotypes. The observed differences in behavioral outcomes between the tMCAO, PTS, and SAH models offer valuable clues regarding the underlying pathophysiological mechanisms involved in stroke-related deficits. Ultimately, these findings contribute to bridging the gap between preclinical stroke research and clinical practice.

Disclosures: S. Tabassum: None. **H. Hu:** None. **S. Wu:** None. **A. Gusdon:** None. **H. Choi:** None. **X.S. Ren:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.26/D11

Topic: C.09. Stroke

Support: CIHR
NSERC

Title: Cortical reorganization and functional recovery in a mouse model of intracerebral hemorrhagic stroke

Authors: A. AURIAT[1], S. CHEVALLIER RUFIGNY[2], S. ALGHARBI[1], R. AVIV[1], ***G. SILASI**[1];
[2]CMM, [1]Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Remodeling of cortical networks is believed to significantly contribute to restoration of function after stroke. Functions of cortical regions damaged by stroke can be overtaken by adjacent structures corresponding to improved functional performance. However, it is unclear to what extent cortical sensory and motor maps reorganize following subcortical injuries, and the extent to which alterations in bilateral motor maps influence long-term functional recovery. Collagenase (ICH) or saline (Sham) was injected into the striatum of Thy1-ChR2 transgenic mice. Lesion evolution was quantified with longitudinal MRI (3 days and 2 weeks) and histology (6 weeks). Sensorimotor deficits were assessed weekly with a battery of behavioural tests, including grid walk, cylinder test, and neurological deficits. Longitudinal optogenetic motor mapping was performed through chronic transcranial windows in order to derive forelimb motor maps from both hemispheres. Forelimb sensory maps were generated by intrinsic optical imaging of cortex in response to a vibroteactile stimulus. Functional deficits persisted for 3 weeks following ICH ($p \leq 0.03$), while motor maps for both contra and ipsi-lesional limbs were depressed for a similar duration . These results suggest that cortical impairments in sensorimotor map representation may be related to the motor disfunction observed following striatal ICH.

Disclosures: A. Auriat: None. **S. Chevallier Rufigny:** None. **S. Algharbi:** None. **R. Aviv:** None. **G. Silasi:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.27/D12

Topic: C.08. Ischemia

Support: CONACYT Grant A1-S-21433 to PDM

Title: Protective effect of diallyltrisulfide on histological damage, motor behavioral and Nrf2 activation on young and old mice subjected to ischemia and reperfusion

Authors: *L. NUÑEZ ORTIZ[1], D. BARRERA-OVIEDO[2], P. MALDONADO[3], C. A. SILVA-ISLAS[4];
[1]Patologia Vascular Cerebral, Inst. Nacional de Neurología y Neurocirugía, México, Mexico; [2]Farmacología, Facultad de Medicina, Univ. Nacional Autónoma de México, Ciudad de Mexico, Mexico; [3]Pharmacol., Facultad de Medicina, Univ. Nacional Autónoma de México, Mexico City, Mexico; [4]Patología Vascular Cerebral, Inst. Nacional De Neurología Y Neurocirugía, Ciudad De México, Mexico

Abstract: Stroke is the second cause of death at a global level and the leading cause of disability, with an increasing incidence in developing countries. Acute ischemic stroke caused by arterial occlusion is responsible for the majority of strokes events. Its management is restricted to restoration of cerebral blood flow with intravenous thrombolysis and/or endovascular thrombectomy, nevertheless, new therapies against the damage induced by biochemical mechanisms such as excitotoxicity, oxidative stress and inflammation, generating during ischemic stroke, with the ability to reduce brain damage, are not approved. Oxidative stress is one of the key mechanisms involved in brain damage, is generated during the ischemia period but also during reperfusion and is a potential target for stroke treatment. In this work we evaluated the effect of diallyltrisulfide (DATS), an antioxidant garlic oil compound on neurological deficit, morphological damage, and activation of Nrf2 pathway in young and older mice exposed to brain ischemia and reperfusion. Male CD-1 mice (3 and 9 months) were subjected to 1 h of middle cerebral artery occlusion (ischemia) and 48.5 h of reperfusion (IR) and administered 3 doses of DATS (15 mg/kg; ip) starting 5 minutes before the onset of reperfusion, and subsequent doses every 24 hours. We evaluated the neurological deficit using 5 tests, the morphological damage in the striatum, and cortex (percent of preserved cells/field) of the penumbral region by hematoxylin and eosin staining and the activation of Nrf2 in striatum by ELISA. We observed that the treatment with DATS (IR+DATS) prevented neurological deficit in young and old mice at 48.5 hours compared with the IR group. Moreover, DATS also showed an increase of viable cells compared to IR group in striatum and cortex. Finally, we observed and increase in Nrf2 activation in the IR and IR+DATS groups in older mice. In conclusion therapeutic administration of DATS decreased the neurological deficit and morphological damage induced by ischemic stroke, in young and older mice, however only Nrf2 activation increase in older mice.

Disclosures: L. Nuñez Ortiz: None. **D. Barrera-Oviedo:** None. **P. Maldonado:** None. **C.A. Silva-Islas:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.28/D13

Topic: C.08. Ischemia

Title: S-allylcysteine protects mice brain tissue against the damage induced by ischemia and reperfusion through the Nrf2 pathway

Authors: *C. A. SILVA-ISLAS[1], J. HIDALGO LOPEZ[3], L. E. NUÑEZ ORTIZ[2], D. BARRERA-OVIEDO[4], A. LOREDO-JASSO[6], P. D. MALDONADO[5];
[1]Patología Vascular Cerebral, Inst. Nacional De Neurología y Neurocirugía, Ciudad De México, Mexico; [2]Patología Vascular Cerebral, Inst. Nacional De Neurología y Neurocirugía, México, Mexico; [3]Patología Vascular Cerebral, Natl. Inst. of Neurol. and Neurosurg., Mexico City, Mexico; [4]Farmacología, Facultad de Medicina, Univ. Nacional Autónoma de México, Ciudad de México, Mexico; [5]Pharmacol., Facultad de Medicina, Univ. Nacional Autónoma de México, Mexico City, Mexico; [6]Ciencias Ambientales y del Suelo, Inst. de Geología, Univ. Nacional Autónoma de México, Ciudad de México, Mexico

Abstract: Acute ischemic stroke (AIS) represents one of the main causes of death and disability in the world; despite this, pharmacological therapies against stroke remain limited. AIS is caused by decreased blood flow to the brain, which results in brain cells damage. The events involved in cell damage and death, include excitotoxicity, oxidative stress, inflammation, microvascular damage, and blood-brain barrier disruption. Oxidative stress plays an important role in cerebral stroke-induced cell damage and the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) confers protection against oxidative stress. The Nrf2 transcription factor is considered the master regulator of antioxidant response. Nrf2 induces the expression of antioxidant and phase 2 enzymes. Some garlic-derived compounds, such as S-allylcysteine (SAC), have the ability to activate Nrf2. The aim of this study was to evaluate the effect of SAC against neurological deficit and Nrf2 activation in a mice model of cerebral ischemia. Male CD-1 mice (3 months) were subjected to 1 hour of ischemia and 48.5 hours of reperfusion (IR). Animals were administered with 3 doses of SAC (100 mg/kg; ip) starting 5 minutes before the onset of reperfusion, and subsequent doses every 24 hours. We evaluated the neurological function using 5 tests, moreover the antioxidant enzymes (SOD1, SOD2 and HO1), Nrf2 and Keap1 levels were evaluated in hippocampus and cortex by western blot, and finally we explored the activation of Nrf2 factor in striatum by ELISA. Results show that SAC administration (IR + SAC) improved neurological function (0.88) at 48 hours compared with the IR group (2.79). SAC administration increased Nrf2, Keap1, SOD1 and HO1 levels in hippocampus and Keap1 levels in cortex. Finally, we found that Nrf2 activation increased in IR+SAC group compared to the IR and CT groups. The present study demonstrates that SAC can activate Nrf2 factor and increases antioxidant enzyme levels, moreover, it improves neurological function in an in vivo model of cerebral ischemia.

Disclosures: C.A. Silva-Islas: None. **J. Hidalgo Lopez:** None. **L.E. Nuñez Ortiz:** None. **D. Barrera-Oviedo:** None. **A. Loredo-Jasso:** None. **P.D. Maldonado:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.29/D14

Topic: C.08. Ischemia

Support: Nebraska State Fund LB692
NIH/NIGMS grant 1P20GM130447
NIH/NIGMS grant 3P20GM130447

Title: Inhibition of BRD4 attenuates global cerebral ischemia-induced neuroinflammation and neuronal death in the hippocampal CA1

Authors: *H. KIM, A. DHULER, R. URQUHART, J.-Y. HWANG;
Pharmacol. and Neurosci., Creighton Univ. Sch. of Med., Omaha, NE

Abstract: Global cerebral ischemia causes selective and delayed death of hippocampal CA1 pyramidal neurons and leads to severe cognitive deficits. Although the damage to hippocampal CA1 pyramidal neurons following global cerebral ischemia is well-documented, the underlying mechanisms and molecular pathways are still not fully understood. To address this, we performed RNA-sequencing on the hippocampal CA1 region at early time points (24 and 48h) in a 4-vessel occlusion (4-VO) rat model to identify the risk factors contributing to delayed neurodegeneration after global cerebral ischemia. Bioinformatic analysis using Ingenuity Pathway Analysis (IPA) revealed immune and inflammatory response-related pathways, including TREM1 signaling, as the top canonical pathways, and a set of genes, including BRD4, as the predicted transcriptional upstream regulators that can regulate these canonical pathways. Because BRD4, an epigenetic reader that recognize acetyl lysine residues, plays a pivotal role in the transcriptional regulation of inflammation and may regulate TREM1 expression, we explored relation between BRD4 and the TREM1 signaling pathway and its impact on global cerebral ischemia-induced neuroinflammation and neuronal death. We first examined whether protein level of BRD4 correlates with changes in TREM1 mRNA and protein expression in hippocampal CA1 by means of RT-qPCR and Western blot analysis. BRD4 was significantly increased at 48 h, and TREM1 mRNA and protein levels were also increased at the same time point after global ischemia. Consistent with this, levels of pro-inflammatory cytokines were significantly increased in the hippocampal CA1 region at 48 h after global ischemia, implicating an increase in TREM1-activated neuroinflammation. Using immunohistochemistry, we found that BRD4 was localized and increased in Iba-1 and CD45 positive cells, suggesting that global cerebral ischemia activates BRD4 in microglia and infiltrating immune cells. Importantly, BRD4 inhibition by JQ1 decreased TREM1 expression and pro-inflammatory cytokines in hippocampal CA1 region in rats subjected to 4-VO. BRD4 inhibition also attenuated gliosis and macrophage M1 polarization, resulting in protection of neurons in hippocampal CA1 region after global cerebral ischemia. Taken together, these findings suggest that BRD4 upregulates TREM1 expression, which in turn enhances neuroinflammation and neuronal death in the hippocampal CA1 after global cerebral ischemia indicating that BRD4-dependent epigenetic regulation of neuroinflammation may be a novel therapeutic target for this devastating neurological disease.

Disclosures: H. Kim: None. **A. Dhuler:** None. **R. Urquhart:** None. **J. Hwang:** None.

Poster

PSTR020: Stroke and Ischemia: Recovery, Behavior and Pharmacological Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.30/D15

Topic: C.08. Ischemia

Support: Korea Drug Development Fund (RS-2023-00218770)
National Research Foundation of Korea (NRF) grant (RS-2023-00242206)

Title: Trehalose-mediated lysosomal enhancement: a promising strategy for mitigating neurotoxicity in acute ischemic brain injury

Authors: *J. LEE, Y.-H. KIM;
Sejong Univ., Seoul, Korea, Republic of

Abstract: Lysosomes play a pivotal role in maintaining cellular health by degrading waste material. However, when lysosomal function and autophagy are impaired, proteins like α-synuclein, hyper-phosphorylated tau, and TDP-43 aggregate, contributing to neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS. Beyond waste disposal, lysosomes also play a role in maintaining intracellular zinc levels, crucial for various cellular processes. In acute brain injuries like stroke, epilepsy, and traumatic brain injury, excitotoxicity—a process involving a surge of zinc ions alongside calcium within neurons—leads to neuronal death. Reactive oxygen species (ROS) exacerbate this by releasing zinc from binding proteins, increasing intracellular zinc levels. The resulting zinc overload triggers a rapid influx into lysosomes, leading to lysosomal membrane permeabilization (LMP), accelerating neurotoxicity. Trehalose, a natural disaccharide composed of two glucose molecules linked by an α-1,1-glycosidic bond, is known to induce transcription factor EB (TFEB) activation and promote lysosomal biogenesis. Given the importance of lysosomes in zinc homeostasis and the ability of trehalose to upregulate lysosomes, this study aimed to investigate whether trehalose could inhibit neuronal death associated with acute brain injury by reducing LMP. Initially, we evaluated the impact of trehalose on lysosomal levels. Starting 4 hours after trehalose treatment, there was a significant increase in lysosomal number and activity, accompanied by TFEB nuclear translocation. In cortical neuronal cultures, trehalose markedly reduced zinc toxicity by decreasing LMP. Furthermore, trehalose protected against other neurotoxicities such as oxidative stress, excitotoxicity and apoptosis. However, these neuroprotective effects were abolished upon treatment with endocytosis inhibitors such as methyl-β-cyclodextrin and chlorpromazine, highlighting the importance of endocytosis in this process. To further assess its neuroprotective potential, trehalose was administered intraperitoneally at a dose of 2 g/kg daily four times and additionally provided in drinking water (3% w/v) for a week before permanent middle cerebral artery occlusion surgery, resulting in a significant reduction in infarct size. Our findings underscore the potential of lysosomal upregulation mechanisms as crucial protective mechanisms not only in neurodegenerative diseases but also in acute brain injuries.

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

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.01/D21

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Tim Reynolds Foundation
NIDILRR (RERC #90RE5021 01 00)

Title: Removal of stimulation artifact from surface EMG for real-time feedback: a step toward optimizing neuromodulation

Authors: *M. RAVI[1], R. PILKAR[2], A. BHEEMREDDY[1], M. ANJARIA[1], G. F. FORREST[1]; [1]Ctr. for Spinal Stimulation, Kessler Fndn., West Orange, NJ; [2]Kessler Fndn., West Orange, NJ

Abstract: Various forms of stimulations such as Spinal Cord Transcutaneous Stimulation (ScTS), neuromuscular electrical stimulation (NMES) etc. are used extensively in neuroscience research and its applications. As more ‘closed-loop’ systems and feedback applications are being developed, visualizing the neuromuscular output during the stimulation is of the utmost importance to harness the true potential of ScTS and NMES as a therapeutic modalities. However, one of the limitations in using surface electromyography (sEMG) for this purpose is the presence of stimulation artifacts that make visualization of sEMG nearly impossible. Building on our previous experience in ‘offline’ removal of stimulation artifact from sEMG, we now present a simple and straightforward framework to do the same in quasi- real-time. Our approach is built on Python-based classical signal processing at the back end with graphical user interfaces (GUI) at the front end that allow for real-time collection, processing, visualization, and feedback of sEMG signals for a single frequency stimulation. Our method involves using an efficient filter consisting of a cascading series of band stop filters at stimulation frequency and its harmonics. We created two GUIs - one for feedback and one for visualization and collected data from healthy participants as well as individuals with Spinal Cord Injury (SCI) performing tasks such as walking on a treadmill with ScTS and Knee Extension with NMES on a Dynamometer. Because of the simplicity of this approach, we were able to scale the application to record, denoise and visualize up to 8 sEMG channels simultaneously at a sampling rate of 10,000 Hz each and with a minimal delay of less than 0.2 seconds overall. The impact of this work lies on the fact that the proposed system can now allow the researchers to tune the stimulation parameters ‘on-fly’ based on the objective sEMG data to achieve the maximal therapeutic outcomes.

Disclosures: M. Ravi: None. **R. Pilkar:** None. **A. Bheemreddy:** None. **M. Anjaria:** None. **G.F. Forrest:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.02/D22

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Reynolds Foundation

Title: Spatiotemporal mapping for a cardiovascular response using spinal cord transcutaneous stimulation in individuals with a spinal cord injury

Authors: *E. HABER[1,2], A. BHEEMREDDY[1], M. B. BAYRAM[1,2], M. RAVI[1], F. ZHANG[1,2], H. SU[3], S. KIRSHBLUM[4,2,5], G. F. FORREST[1,2];
[1]Kessler Fndn., west orange, NJ; [2]Rutgers New Jersey Medical School, Newark, NJ; [3]Sch. of Computing, Montclair State Univ., Montclair, NJ; [4]Kessler Inst., West Orange, NJ; [5]Kessler Foundation, West Orange, NJ

Abstract: Spinal cord transcutaneous stimulation (scTS) presents a promising avenue for improving cardiovascular regulation in individuals with high-level spinal cord injuries (SCI), tackling the challenges of fluctuating blood pressure (BP) and associated symptomatic hypo- and hypertensive episodes. A limiting factor of many stimulation studies is the lack of validation in choosing sites and parameters for stimulation. Our study seeks to address this issue by evaluating a 'spatiotemporal mapping' procedure for scTS. Specifically, we identified target parameters for eliciting a BP response through stimulation across different spinal segments. We present findings from a case series involving eight male individuals with a chronic cervical SCI, investigating the effects of scTS on C3/4, C4/5, C5/6, C6/7, C7/T1, T1/2, T11/12, L1/2, and S1/2 . Each participant underwent a single day of mapping, comprising multiple consecutive trials, each targeting a different spinal segment. Stimulation was administered using Neo-Stim 5, a five-channel constant current stimulator. BP was continuously measured using Finapres finger cuff (Finapres Medical Systems, Amsterdam, the Netherlands) and calibrated with brachial BP measures. Statistical analysis was conducted using repeated measures analysis of variance (ANOVA) with post-hoc pair-wise comparisons. We found that stimulation of the lower segments, i.e., T11/12, L1/2, and S1/2, using monophasic rectangular pulses with a duration of 1 ms, at a frequency of 30 Hz, and a carrier frequency of 5 kHz, resulted in a notably increased BP, compared to stimulation at cervical or high thoracic spinal segments, or using lower frequencies. This observed consistent trend across participants underscores the potential efficacy of lumbosacral sites in modulating BP. These findings can guide future scTS studies aimed at improving cardiovascular function and addressing autonomic impairment in individuals with SCI.

Disclosures: E. Haber: None. **A. Bheemreddy:** None. **M.B. Bayram:** None. **M. Ravi:** None. **F. Zhang:** None. **H. Su:** None. **S. Kirshblum:** None. **G.F. Forrest:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.03/D23

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Augmenting stand activity-based training with dynamic tasks in the presence of spinal cord epidural stimulation: A Case Study

Authors: *M. B. BAYRAM, G. F. FORREST;
Kessler Fndn., West Orange, NJ

Abstract: Targeted spinal cord epidural stimulation (scES) combined with activity-based training (ABT) has been shown to improve the recovery of motor functions for individuals with complete or incomplete spinal cord injury (SCI). Standard stand ABT, for individuals with SCI while using scES , is comprised of sit-to-stand and standing with minimal external manual assistance for as long as possible. This case study adds various upper and lower limb exercises to stand ABT, to examine the effect, quantified by the exercise type, repetitions, and average time to complete the repetition per exercise.
A female research participant with cervical spinal cord injury, 28 months post epidural implant and after 100 sessions of stand ABT, was recruited. She was asked to do lower limb (bilateral weight shifts - BWS or single leg knee extension/flexion - SLKEF) or upper limb (single arm upward reach - SAUR or single arm lateral reach - SALR) exercises, every 10 minutes, while standing. She stood 2 hours per day, 4 days per week.
A total of 28 stand ABT sessions with exercises were completed. BWS and SAUR exercises were always completed with the given number of repetitions whereas SLKEF and SALR gradually increased. Average time (mean±SD, in seconds) to complete the given exercise was consistent for BWS (13.2±0.3) and SAUR (5.7±0.4) but not for SALR (5.1±1.2) or SLKEF (7.9±2.1). The total standing time was positively correlated with the number of exercises completed or attempted.
ABT with scES has a positive effect on the recovery of functions for individuals with SCI. It was also shown that increasing the difficulty of motor tasks by combining periods of multi-focused tasks promotes improvement. This case provides evidence that challenging the spinal circuitry with various dynamic tasks during standing ABT with scES has the potential to increase the motor recovery in individuals receiving stand ABT. The potential of combining stand ABT with various exercises could have the same effect.

Disclosures: M.B. Bayram: None. **G.F. Forrest:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.04/D24

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Tim Reynolds Foundation
Ritholz Foundation

Title: Reduction of Spasticity on EMG in the Time and Frequency Domain for Treadmill Walking with Spinal Cord Injury

Authors: *A. BHEEMREDDY[1], M. ANJARIA[2], M. B. BAYRAM[2], M. RAVI[2], F. ZHANG[2], G. F. FORREST[2];
[1]Kessler Fndn., West Orange, NJ; [2]Reynolds Ctr. for Spinal Stimulation, Kessler Fndn., West Orange, NJ

Abstract: Spinal Cord Injury (SCI) in 65-70% of cases leads to the development of spasticity within one-year post-injury. Spinal cord transcutaneous stimulation (scTS) with activity-based training (ABT) improves function for people with SCI. With continued stimulation combined with training, there is a reduction in spasticity. Targeted stimulation with specific parameters of stimulation can also have a direct and immediate effect on spasticity. This study applied targeted scTS to specific sites during assisted treadmill stepping with body weight support (BWS). Surface electromyogram (EMG) (Motion Lab Systems Inc., Baton Rouge, LA) for trunk and bilateral lower limb muscles determined muscle activation during stepping to examine the changes in muscle activity for single session data. The study also evaluated the long-term effect of scTS training on spasticity. Clinical measures for spasticity were also collected. Continuous Wavelet Transform (CWT) determined the time- and frequency-domain of the EMG features to accurately classify and identify different frequency characteristics of muscle activation (spasticity). CWT of our data showed relevant frequency content unrelated to scTs frequency for single site stimulation. The power of the EMG signal collected during stepping tended to be shifted with stimulation compared to without stimulation. A more apparent distinction between on and off periods of muscle activity in both time and frequency domains was distinctly present with targeted scTS for stepping concurrent to a decrease in clinical measure of spasticity (compared to baseline stepping without scTS). Continuous Wavelet Transform combined with clinical measures for spasticity suggests that stimulation parameters can directly and immediately affect spasticity.

Disclosures: A. Bheemreddy: None. **M. Anjaria:** None. **M.B. Bayram:** None. **M. Ravi:** None. **F. Zhang:** None. **G.F. Forrest:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.05/D25

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Ritholtz Foundation
Tim Reynolds Foundation

Title: Sequential spinal cord transcutaneous stimulation protocol enables voluntary motor function.

Authors: *M. ANJARIA, A. BHEEMREDDY, M. RAVI, M. B. BAYRAM, F. ZHANG, G. F. FORREST;
Kessler Fndn., West Orange, NJ

Abstract: Targeted spinal cord transcutaneous stimulation(scTS) with overground gait training can facilitate increased coordination profiles for lower limb kinematics in individuals with spinal cord injury (SCI). Neurophysiological spinal mapping determines the sites and parameters of spinal stimulation. Spinal mapping for voluntary and stepping activities determines targeted stimulation profiles for increased intra and inter-limb coordination of lower extremity muscle activity. This study evaluated the immediate and long-term effect of sequential stimulation of spinal sites on lower extremity motor pools for motor complete and incomplete spinal cord injury participants. For each trial, multiple sequential targeted scTS were (1ms pulse, rectangular waveform) delivered using cathodes at differing cervical and lumbosacral spinal sites with respective anodes. Before and after training, clinical measures were collected. Full-body kinematics (Optitrak, Oregon) were collected during body weight supported(BWS) treadmill stepping with and without scTS. EMG (Motion Lab Systems Inc., Baton Rouge, LA) was collected for both upper and lower extremity muscle groups. In addition, the immediate and continuous real-time effect of spinal stimulation on spatial-temporal changes for EMG (amplitude and timing) during treadmill stepping were determined. Results determined distinct changes in EMG parameters with sequential single and combined stimulation of spinal sites, enabling improved step kinematics. Long-term training protocol resulted in changes with and without stimulation. These are preliminary results of the effect of sequential stimulation on recovery.

Disclosures: M. Anjaria: None. **A. Bheemreddy:** None. **M. Ravi:** None. **M.B. Bayram:** None. **F. Zhang:** None. **G.F. Forrest:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.06/D26

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NJCSCR (CSCR23ERG001)
NJCSCR (CSCR23FEL002)

Title: Feasibility of Implementing a Transcutaneous Spinal Stimulation Research Protocol in an Inpatient Rehabilitation Setting for Individuals with Subacute Spinal Cord Injury

Authors: *J. CARNAHAN[1], M. AGOSTINI[1], F. ZHANG[1], E. HABER[1], R. ZELENY[1], D. PEPE[1], M. RAVI[1], A. BHEEMREDDY[1], M. ANJARIA[2], M. B. BAYRAM[2], B. SNIDER[3], S. KIRSHBLUM[3], G. F. FORREST[1];
[1]Tim and Caroline Reynolds Ctr. for Spinal Stimulation, Kessler Fndn., West Orange, NJ; [2]Tim & Caroline Reynolds Ctr. for Spinal Stimulation, Kessler Fndn., West Orange, NJ; [3]Kessler Inst., West Orange, NJ

Abstract: Spinal cord injury (SCI) affects approximately 18,000 individuals annually, leading to significant morbidity and mortality. Acute inpatient rehabilitation settings provide a unique opportunity to conduct research and improve outcomes. However, implementing research protocols in these settings can be challenging. Length of stay on average in an inpatient rehabilitation setting is 30 days. The 3-hour rule for therapy must be adhered to and medical and nursing needs take precedence. Additionally, these individuals are psychologically and physiologically adjusting to their new injuries. Finally, common medical complications associated with acute spinal cord injury, including but not limited to deep vein thromboses, vertebral artery dissections, wounds, fractures, severe bradycardia, and use of mechanical ventilation, pose potential safety risks for participation in stimulation studies.Data is being collected from patients admitted to Kessler Institute for Rehabilitation (KIR) in West Orange, NJ and have consented to be contacted for studies. Two studies using spinal cord transcutaneous stimulation (scTS) are being evaluated for feasibility: neuromodulation of blood pressure using scTS (BP) and scTS combined with activity-based training of the upper extremity (UE). Patients are eligible for inclusion into one or both studies if they are < 8 weeks post injury and medically stable. Eligibility for UE also includes SCI level C2-C7 AIS A, B, or C and BP includes SCI level up to and including T2. Feasibility is evaluated based on recruitment rates, data completeness, and protocol adherence. The research protocols consist of baseline assessments (pre) and post training re-assessments (post). UE additionally consists of 10 training sessions and follow-ups at 1-month, 2-months, and 3-months (FU). To date a total of 4 participants have enrolled into these two studies, with 1 participant enrolling into both. Preliminary data suggests overall enrollment is 6% of individuals admitted to KIR that meet inclusion criteria for one or both studies, completion is 100% for BP and 50% for UE, and FU 0%. This study is ongoing. Additional data to be collected and reported.

Disclosures: J. Carnahan: None. **M. Agostini:** None. **F. Zhang:** None. **E. Haber:** None. **R. Zeleny:** None. **D. Pepe:** None. **M. Ravi:** None. **A. Bheemreddy:** None. **M. Anjaria:** None. **M.B. Bayram:** None. **B. Snider:** None. **S. Kirshblum:** None. **G.F. Forrest:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.07/D27

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Christopher and Dana Reeve Foundation
Kessler Foundation
University of Louisville Hospital
Medtronic
The Leona M. and Harry B. Helmsley Charitable Trust

Title: Changes in Trunk independence following Stand Training with spinal cord epidural stimulation in Cervical SCI: Two Case Studies.

Authors: *C. ANGELI[1], E. REJC[2,3], G. F. FORREST[1], S. J. HARKEMA[4];
[1]Tim and Caroline Reynolds Ctr. for Spinal Stimulation, Kessler Fndn., West Orange, NJ; [2]Med., Univ. of Udine, Udine, Italy; [3]Tim and Caroline Reynolds Center for Spinal Stimulation, Kessler Foundation, West Orange, NJ; [4]KSCIRC, Univ. of Louisville, Louisville, KY

Abstract: Most individuals with motor complete spinal cord injury are unable to stand independently without external assistance. Activity Based Recovery Training (ABRT) promotes reactivation of the neuromuscular system below the level of injury. In addition, spinal cord epidural stimulation (scES) allows for the integration of sensory information leading to the modulation of motor output in the lower extremities. We present a comparison of two case studies proving evidence of the progression of recovery of trunk control during standing with scES and the reliance on upper limb support during standing. One individual (C3 AIS-A) was able to regain independent trunk control and recovered some ability to stand without upper extremity support when assisted at the hips. The second individual (C4 AIS-A) had shorter bouts of trunk independence and always required upper extremity support. Both individuals received 2 hours of stand ABRT with scES for 160 sessions. Participants were assessed prior to the start of training (pre-intervention), after 80 sessions (post intervention 1) and after 160 sessions (post intervention 2). Both participants required trunk assistance in addition to upper limb support to maintain proper trunk kinematics at the pre-intervention time point. This was illustrated by lower forces with a lower coefficient of variation (c.v.) generated through upper extremities compared to periods of independent trunk with upper extremity support. The individual that achieved the greatest level of trunk independence, average of 52 min during intervention 1 and 98 mins during intervention 2, showed a reduction in vertical forces placed through the upper extremities and a reduction in the c.v. when comparing post intervention 2 to post intervention 1. In contrast, the individual with an average of 22 min and 30 min of trunk independence across training sessions during intervention 1 and 2 respectively, showed limited difference in vertical upper extremity force and c.v. at both time points. Results from this investigation demonstrate the ability to improve trunk control following standing ABRT with scES and decrease the reliance on upper extremity support to maintain proper trunk posture in individuals with a cervical motor complete injury. We show that increased trunk independence time has a tendency to reduce the amount of upper extremity support, hinting towards increased activation of trunk musculature for proper posture. Hereby providing evidence that scES modulates network excitability of the injured spinal cord leading to integration of afferent input to activate trunk and lower extremity muscles and improve independence during stable standing.

Disclosures: C. Angeli: None. **E. Rejc:** None. **G.F. Forrest:** None. **S.J. Harkema:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.08/D28

Topic: C.11. Spinal Cord Injury and Plasticity

Support: New York State Spinal Cord Injury Research Board under Grant C31290GG
Kessler Foundation
Christopher and Dana Reeve Foundation
Leona M. & Harry B. Helmsley Charitable Trust
UofL Health - University of Louisville Hospital
Medtronic Plc

Title: Effects of trunk perturbation magnitude and direction knowledge on standing postural responses in individuals with spinal cord injury receiving epidural stimulation

Authors: *E. REJC[1,2], C. D. BOWERSOCK[3,4], T. PISOLKAR[3], S. ZACCARON[1], C. A. ANGELI[5], G. F. FORREST[5], S. AGRAWAL[6], S. J. HARKEMA[3];
[1]Univ. of Udine, Udine, Italy; [2]Kessler Foundation, West Orange, NJ; [3]Kentucky Spinal Cord Injury Res. Ctr., Univ. of Louisville, Louisville, KY; [4]Northern Arizona University, Flagstaff, AZ; [5]Kessler Fndn., West Orange, NJ; [6]Columbia Univ., New York, NY

Abstract: Objective. Individuals with motor complete spinal cord injury (SCI) receiving tonic spinal cord epidural stimulation to facilitate standing (scES) can generate lower limb postural responses and can improve standing postural control following robotic postural training. Here, we assessed the effects of (i) trunk perturbation magnitude and (ii) participants' knowledge of perturbation direction on standing postural responses. Methods. Six individuals with chronic motor complete SCI, already implanted with a scES unit, participated in this study. Lateral, front, and back trunk perturbations were delivered by the robotic upright stand trainer (RobUST) while participants were standing with scES and free hands. Three perturbation magnitudes (10±4% -Low, 14±4% -Mid, and 18±4%BodyWeight -High) were tested 4 times for each direction in a randomized order; perturbation direction was not disclosed. Participants also received 4 perturbations (14±4%BodyWeight) for each cardinal direction while already knowing where RobUST would pull their trunk. Trunk displacement, ground reaction forces (GRF), and EMG activity of lower limb muscles were assessed. Results. Perturbation magnitude significantly affected trunk displacement and GRFs in all tested directions (p values between 0.002 and <0.001), with larger modulations elicited by higher magnitudes. For example, during lateral perturbations, trunk displacement with Mid- and High-magnitude was 82% and 163% larger than with Low. Similarly, ipsilateral vertical GRF with Mid- and High-magnitude was 14% and 23% larger than with Low. Lower limb EMG amplitude responses were less consistent. No significant differences were observed between Low- and Mid-magnitude. Conversely, High-magnitude could promote either larger EMG responses (e.g., Tibialis Anterior, Back perturbation) or somewhat disrupted responses resulting in lower EMG amplitude (e.g., ipsilateral Vastus Lateralis, Lateral) compared to weaker perturbations. Disclosure of perturbation direction

promoted significantly smaller trunk displacement in Lateral (-23%) and Back (-54%) perturbations, smaller GRF modulation in Lateral, and no effect on EMG. Conclusion. Trunk displacement and GRF showed relevant modulations that were consistent with changes in perturbation characteristics. Conversely, lower limb EMG could show opposite amplitude responses to High perturbations, and were not affected by the knowledge of their direction. These findings contribute to characterize the residual postural control potential of the spinal circuitry below the level of SCI and should be considered when defining postural training protocols.

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Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.09/D29

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Tim Reynolds Foundation

Title: Microstructural changes induced by spinal cord transcutaneous stimulation revealed by DTI in spinal cord injury

Authors: *N. BRIHMAT[1], S. H. SALEH[2], M. B. BAYRAM[3], F. ZHANG[4], J. CARNAHAN[5], G. H. YUE[6], G. F. FORREST[4];
[1]Reynolds Ctr. for Spinal Stimulation, Kessler Fndn., West Orange, NJ; [2]Rutgers, The State Univ. of New Jersey, Newark, NJ; [3]Tim & Caroline Reynolds Ctr. for Spinal Stimulation, Kessler Fndn., West Orange, NJ; [4]Kessler Fndn., West Orange, NJ; [5]Caroline and Tim Reynolds Ctr. for Spinal Stimulation, Kessler Fndn., Ridgewood, NJ; [6]Human Performance and Engin., Kessler Fndn. Res. Ctr., West Orange, NJ

Abstract: Neuroimaging is increasingly being suggested to be used an informative tool to highlight changes induced by a spinal cord injury (SCI), recovery or therapeutic intervention. Among the MRI techniques, diffusion tensor imaging (DTI) measures water diffusion and its directionality within white matter fibers tracts and thus can inform about the integrity and microstructural changes within important corticospinal pathways. Here, we used DTI to evaluates changes in response to spinal cord transcutaneous stimulation (scTS)-based motor training in chronic SCI participants. Data were obtained from one male (24 y.o.), with complete (ASIA A), cervical (C4) and chronic (4 years) SCI, in the context of an ongoing 3-arm, multicenter, open-label RCT. The protocol consists of a baseline assessment (Pre), 60 sessions of scTS-based intervention, re-assessment post-intervention (Post) and at 1 mo follow-up (FU). During the intervention, the participant received upper-extremity (UE) task-specific motor training with continuous targeted scTS applied depending on tolerability and deficits. UE

sensorimotor function was assessed using the GRASSP scale. DTI was acquired and tractometry analysis (tract volume in mm^3, fractional anisotropy, FA) was performed using DSI-Studio to examine mircrostructural changes and integrity of the corticospinal tract (CST) and reticulospinal tract (RST). By the end of the scTS-based training, UE sensorimotor function increased importantly for both sides ($\Delta GRASSP_{Post-Pre} = +33$), changes that were still observed at 1 mo follow-up ($\Delta GRASSP_{Fu-Pre} = +20$). Progressive increases in CST and RST volume were observed bilaterally across time of assessment; and increases in mean FA were measured mainly for the right CST and RST, with more significant increases caudally. The preliminary results favor pathways microstructural changes in response to the intervention in chronic SCI. Increases in FA may reflect recovery induced by the scTS-based training and the involvement of these tracts in such processes. Such results favor the use of DTI as additional objective tool for evaluating effects of injury and therapeutic interventions.

Disclosures: **N. Brihmat:** None. **S.H. Saleh:** None. **M.B. Bayram:** None. **F. Zhang:** None. **J. Carnahan:** None. **G.H. Yue:** None. **G.F. Forrest:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.10/D30

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ES_BI-2017, Christopher and Dana Reeve Foundation

Title: Effects of sitting trunk training and stand training with epidural stimulation on sitting trunk kinematics in individuals with chronic motor complete spinal cord injury.

Authors: *K. JOSHI[1], E. REJC[2], S. J. HARKEMA[3], C. A. ANGELI[4];
[1]Bioengineering, Univ. of Louisville, Louisville, KY; [2]Med., Univ. of Udine, Udine, Italy; [3]KSCIRC, Univ. of Louisville, Louisville, KY; [4]Kessler Fndn., West Orange, NJ

Abstract: Spinal cord epidural stimulation (scES) as well as activity-based training have the potential to improve seated postural control in individuals with spinal cord injury (SCI). Past evidence also suggests that stand training could lead to improved postural control outcomes. Hence, we compared the effects of sitting trunk-specific training with scES and trunk-specific plus stand training with scES on trunk kinematics in seated tasks. Sixteen individuals with cervical SCI (Age: 37.1 ± 12.1 yrs; time post-injury: 11.2 ± 8.2 yrs) implanted with a scES unit were randomized into: Voluntary - Vol (Group 1); or Vol and Stand (Group 2). Each group performed two 80-session interventions. Vol intervention comprised tasks to improve seated trunk control. Group 1 crossed over to Vol and Stand in the second intervention. Each individual performed tall-sit, sagittal plane leans, and frontal plane leans with Vol-scES at 3 time-points (Post Implant, Post Int1, and Post Int2). Center of mass of pelvis and trunk were obtained from full-body kinematics. Six postural control outcomes were then computed: anterior-posterior

(TAPD) and lateral trunk displacement (TLD), and trunk velocity in all four directions (anterior-TAV, posterior-TPV, left-TLV, and right-TRV). Improved outcomes were defined as decreases in all velocities and displacements in all tasks, except for an increase in displacement in the direction of movement in leaning tasks. In tall-sit, both intervention sets tended to decrease postural control for both groups, except Group 2 had TLV and TRV decreases after the second intervention while TAV decreased following Vol and Stand training for both groups. In sagittal plane lean, TAV and TPV tended to decrease for Group 1 after Vol and Stand training suggesting that stand training may have supplemented postural control improvements. For Group 2, TAV tended to decrease after the first intervention and TAPD increased after both intervention sets. In frontal plane lean, all velocities and TAPD tended to decrease for Group 1 after Vol only training while only TAV, and TRV improved after Vol and Stand training, suggesting that added stand training had a limited effect on lateral control. For Group 2, TAV, and TPV tended to decrease after the first intervention, while TLV, and TRV tended to decrease after the second intervention. The addition of stand training post voluntary training tended to have a greater effect on postural control in sagittal plane lean task, while both groups showed similar improvements in frontal plane lean. These results further our understanding of task-specificity during training interventions and aid in developing better rehabilitation protocols.

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Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.11/D31

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Kessler Foundation

Title: Lowe extremity Neural Activation Changes during 30 minutes of standing with spinal cord epidural spinal stimulation in Cervical SCI: Case

Authors: *G. F. FORREST[1], C. A. ANGELI[1], S. J. HARKEMA[2], E. REJC[3];
[1]Kessler Fndn., West Orange, NJ; [2]KSCIRC, Univ. of Louisville, Louisville, KY; [3]Med., Univ. of Udine, Udine, Italy

Abstract: Individuals with a complete spinal cord injury completed 30 minutes of standing experiment with targeted cohorts for standing with cord epidural stimulation in Cervical SCI(AIS C, C5/6) The activation changes on lower extremity motor pools

Disclosures: G.F. Forrest: None. **C.A. Angeli:** None. **S.J. Harkema:** None. **E. Rejc:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

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Program #/Poster #: PSTR021.12/D32

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NJCSCR Grant CSCR23ERG001
NIDILRR (RERC #90RE5021-01-00)
NIDILRR (ARRT #90ARHF0002)
the Tim Reynolds Foundation

Title: Effects of Combining Spinal Cord Transcutaneous Stimulation with Activity-based Training versus Training Only on Spinal Excitability in Individuals with Tetraplegia

Authors: *F. ZHANG[1], J. CARNAHAN[2], M. AGOSTINI[1], A. BHEEMREDDY[3], M. RAVI[3], M. ANJARIA[3], G. F. FORREST[1];
[1]Kessler Fndn., West Orange, NJ; [2]Caroline and Tim Reynolds Ctr. for Spinal Stimulation, Kessler Fndn., Ridgewood, NJ; [3]Ctr. for Spinal Stimulation, Kessler Fndn., West Orange, NJ

Abstract: Spinal cord transcutaneous stimulation (scTS) is a non-invasive neuromodulation technique that stimulates the spinal circuitries from skin surface via an electrical current flow. Previous studies have suggested that scTS can increase the excitability of spinal networks, and in turn bring interneurons and motor neurons closer to motor threshold to facilitate the impaired descending drive following spinal cord injury (SCI). Combining scTS with activity-based training (ABT) that can promote activity-dependent neuroplasticity holds great therapeutic potential to lead to sustained changes in neural network and long-term functional recovery. The goal of this study is to quantify and characterize the pre-post changes of spinal excitability in individuals with cervical SCI after receiving the intervention of scTS+ABT, as compared to ABT only. ABT focused on repetitive unimanual activities of gross upper extremity (UE) movement, grasping, and pinching without bilateral facilitation involved. In scTS+ABT, sub-motor-threshold, tonic scTS (biphasic, rectangular pulses with 1ms duration, filled with a carrier frequency of 5kHz) with optimized intensity and frequency was delivered at the cervical and thoracic spinal segments over the dorsal skin while ABT was administered. Spinal excitability was tested before and after the completion of intervention by measuring the evoked response in UE muscles with increasing spinal stimulation intensity. Stimulation was delivered at spinal segments above and below the lesion over the dorsal skin when participants remained at rest in the supine position with both arms resting along the body. Peak-to-peak analysis was performed to evaluate the recruitment curve of motor response, with two metrics extracted: (1) the excitation threshold which indicates the excitability to the initial recruitment of spinal motor neurons, and (2) the maximum slope of recruitment curve which indicates the excitability of spinal motor neurons relative to the increasing stimulation intensity (gain). We observed mixed results of elevated and reduced spinal excitability in different motor pools and body sides following the intervention of scTS+ABT, with greater changes in scTS+ABT over ABT alone. The reduced excitability may result from an increased activation of the inhibitory inter-neuronal circuitry following scTS+ABT , which leads to reduction of hyperactivity in neural networks and greater improvements in UE function recovery. This research is expected to provide preliminary

data for a larger clinical trial to understand the neurological mechanisms underlying the combined neuromodulation intervention for SCI rehabilitation.

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Poster

PSTR021: Spinal Cord Injury: Recovery

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Program #/Poster #: PSTR021.13/D33

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Kessler Foundation
Leona M. & Harry B. Helmsley Charitable Trust
University of Louisville Hospital
Medtronic Plc
Christopher & Dana Reeve Foundation

Title: Follow-up of orthostatic tolerance in individuals with chronic spinal cord injury after long-term intervention with lumbosacral spinal cord epidural stimulation

Authors: *S. WANG[1], C. A. ANGELI[2], E. REJC[3], J. M. WECHT[4], G. F. FORREST[2], O. BLOOM[5], J. WEIR[6], P. D. SHARMA[7], S. WAGERS[8], M. BOAKYE[9], S. KIRSHBLUM[10], N. Y. HAREL[11], J. D. GUEST[12], S. WU[13], S. J. HARKEMA[14];
[1]Kentucky Spinal Cord Injury Res. Ctr., Dept. of Neurolog. Surgery, Univ. of Louisville, Louisville, KY; [2]Kessler Fndn., West Orange, NJ; [3]Med., Univ. of Udine, Udine, Italy; [4]Spinal Cord Injury Res., James J Peters VA Med. Ctr., Nyack, NY; [5]Mol. Med.; Physical Med. and Rehabil., The Feinstein Inst. For Med. Res., Manhasset, NY; [6]Univ. of Kansas, Lawrence, KS; [7]Kentucky Spinal Cord Injury Res. Ctr., Univ. of Louisville, Louisville, KY; [8]Kentucky Spinal Cord Injury Res. Ctr., Div. of Physical Med. and Rehabil., Univ. of Louisville, Louisville, KY; [9]Neurosurg., Univ. of Louisville, Louisville, KY; [10]Kessler Inst., West Orange, NJ; [11]Neurology; Rehabil. and Human Performance, James J. Peters VA Med. Ctr., Bronx, NY; [12]Neurolog. Surgery/Miami Project to Cure Paralysis, Univ. of Miami Miller Sch. of Med., Miami, FL; [13]Biostatistics, Univ. of Florida, Gainesville, FL; [14]Kentucky Spinal Cord Injury Res. Ctr., Neurolog. Surgery, Univ. of Louisville, Louisville, KY

Abstract: Introduction: Cardiovascular dysfunction is common after cervical spinal cord injury (SCI), manifesting as episodic life-threatening high blood pressure (autonomic dysreflexia), persistent low blood pressure, and orthostatic hypotension. The cardiovascular abnormalities reflect disrupted supraspinal sympathetic input and maladaptation in the spinal circuitry caudal to the injury. We reported that lumbosacral spinal cord epidural stimulation optimized for cardiovascular function (CV-scES) mitigates orthostatic hypotension in individuals with chronic, cervical SCI, acutely before they received CV-scES intervention. Here we report the effect of

CV-scES on orthostatic tolerance following long-term scES intervention. **Methods:** Thirty-two participants with chronic cervical SCI and orthostatic hypotension underwent implantation of a Medtronic Intellis stimulator with a 16-electrode array over dorsal lumbosacral spinal segments. Electrical stimulation parameters were established to maintain systolic blood pressure between 110-120 mmHg without evoking lower extremity muscle activity (CV-scES), or to facilitate trunk stability and lower extremity voluntary movement (Vol-scES), or to facilitate standing (Stand-scES). Participants were then randomized into one of four intervention groups: CV-scES for 6 hours daily; CV-scES for 6 hours and Stand-scES with stand training for 2 hours daily; Vol-scES with trunk and leg exercises for 6 hours daily; and Vol-scES with trunk and leg exercises for 6 hours and Stand-scES with stand training for 2 hours daily, 5 times per week. The orthostatic tolerance test, 70° head-up tilt for up to 30 minutes, was performed with and without CV-scES activated during tilt, at pre- and post-intervention. **Results:** All individuals of the four groups, except for one individual, maintained 30 minutes at upright position post-intervention, with CV-scES activated during tilt. Six individuals increased their duration of tilt time from 6.7 +/- 5.2 minutes to 30 minutes without stimulation during tilt (n=1 CV-scES group; n=2 in the CV-scES + Stand-scES group; n=1 in Vol-scES group and n=2 in the Vol-scES + Stand-scES group). **Conclusions:** CV-scES stabilizes blood pressure regardless of the neuromodulation training intervention. Some individuals improved orthostatic intolerance even without stimulation. These results indicate that targeted stimulation for cardiovascular function is a viable intervention for severe chronic cervical SCI.

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Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.14/D34

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Lumbosacral spinal cord epidural stimulation reduces blood pressure instability by attenuating spasms of lower limb muscles

Authors: *P. P. SHARMA[1], S. WANG[2], C. A. ANGELI[3], G. F. FORREST[3], E. REJC[4], M. BOAKYE[5], S. J. HARKEMA[6];
[1]Univ. of Louisville, Louisville, KY; [2]Kentucky Spinal Cord Injury Res. Ctr., Univ. of Louisville, Louisville, KY; [3]Kessler Fndn., West Orange, NJ; [4]Med., Univ. of Udine, Udine, Italy; [5]Neurosurg., Univ. of Louisville, Louisville, KY; [6]KSCIRC, Univ. of Louisville, Louisville, KY

Abstract: Introduction: Cardiovascular dysfunction after cervical spinal cord injury (SCI) results in blood pressure instability from persistent hypotension, episodes of high blood pressure (autonomic dysfunction) and orthostatic hypotension. We reported that continuous lumbosacral spinal cord epidural stimulation targeted for cardiovascular function (CV-scES) stabilizes the systolic blood pressure during daily activities and ameliorates orthostatic hypotension. We observed additional rapid increases in the systolic blood pressure when individuals had spasms. We hypothesized that epidural stimulation targeting spasm reduction (SP-scES) would prevent the increase in systolic blood pressure. **Methods:** Preliminary data was collected from two cervical SCI participants who underwent implantation of a 5-6-5 Medtronic epidural stimulation electrode array over the lumbosacral spinal cord. While in the relaxed seated position in a wheelchair, hemodynamic data was collected using a three-lead ECG (Finapres Medical Systems, Amsterdam, Netherlands) and beat-to-beat blood pressure recorded from the index finger, middle finger, or thumb using photoplethysmography (Finapres Medical Systems, Amsterdam, Netherlands). We identified CV-scES parameters that stabilized the blood pressure instability and SP-scES parameters that reduced the duration and severity of spasms. We also recorded changes in the lower limb muscle activity. **Results:** When the initiation of the spasm was recognized, we immediately changed from CV-scES program to SP-scES program. We observed significant and early reduction in the leg muscle activity and systolic blood pressure compared to maintaining CV-scES program alone. **Conclusions:** Besides sympathetic overactivity, the presented result demonstrates that blood pressure instability following SCI can also occur due to muscle spasms. Specific lumbosacral epidural stimulation strategies targeting cardiovascular function and lower limb spasms can effectively reduce blood pressure instability.

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Poster

PSTR021: Spinal Cord Injury: Recovery

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.15/D35

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant NS110605
NIH Grant NS055976

Title: Dura Repair changes Macrophage/Microglia Population Levelsatthe Injury Site and Influences Locomotor Recovery after SCI

Authors: *J. PAZ AMAYA[1], M. A. LEMAY[1], E. ABBOTT[2];
[1]Bioengineering, Temple Univ., Philadelphia, PA; [2]Biomed. Engin., Duke Univ., Durham, NC

Abstract: Recently, evidence has been shown for spontaneous locomotor recovery after complete SCI in the feline model. These findings have led to some questioning of the feline

model as an SCI model. However, the lack of standardized procedures for spinal transection in cats, i.e. whether the dura matter is spared or cut during transection, may explain some of the reported differences in recovery. The dura matter protects the cord but if compromised it can expose the neural tissue to exogenous factors, radically changing the cellular and molecular landscape and potentially leading to different behavioral outcomes. We hypothesized that transecting the dura leads to spontaneous locomotor recovery due to a higher concentration of BDNF-secreting microglia associated with a higher immune response at the site of injury. A group of 8 cats received an SCI at the T11-T12 spinal segment. The control group (n=4) had their dura repaired immediately after transection while the experimental group (n=4) had their dura completely cut along with the cord. Locomotor recovery was evaluated at 3- and 5-weeks post-transection using motion capture. On average, subjects with a transected dura were able to achieve higher speeds during treadmill locomotion at 3 and 5 weeks after injury. At 6 weeks, the spinal cord tissue was retrieved and sectioned for histological analysis. Cross sections of the cord just caudal to the site of injury were stained using calcium-binding protein Iba-1 as a marker for microglia/macrophages. Intensity analysis revealed that the group with a transected dura had significantly less Iba-1 stain per μm^2, indicating a lesser immune response. Contrary to our initial hypothesis, the present study shows that transecting the dura is associated with less microglia/macrophage presence at the site of injury. Our results are congruent with reports of elevated immune responses limiting recovery after SCI, further arguing that a standard methodology for spinal transection in the feline model is necessary to compare treatment efficacy across studies.

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Poster

PSTR021: Spinal Cord Injury: Recovery

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Program #/Poster #: PSTR021.16/D36

Topic: C.11. Spinal Cord Injury and Plasticity

Support: The Guillian Reny Stepping Strong Center for Trauma Innovation

Title: Transplantation of spinal motor neurons to prevent permanent loss of function in rat sciatic nerve injury model

Authors: *A. MISTRY[1,2], S. BAZAREK[3], L. CAPANO[2], A. H. HELD[2], B. WAINGER[2]; [2]Neurol., [1]Massachusetts Gen. Hosp., Boston, MA; [3]Case Western Reserve Univ., Cleveland, OH.

Abstract: Traumatic peripheral nerve injuries can result in devastating loss of muscular function and are one of the most challenging injuries from which to recover. While axons within injured nerve can regenerate, distal tissue, specifically the neuromuscular junctions (NMJs) and muscle, degenerate faster, hindering the recovery process and leading to irreversible muscle atrophy. In

the clinic, functional and “babysitting” nerve transfers are utilized to restore function and preserve muscle mass, respectively. A functional nerve transfer can permanently replace the severed nerve if a viable donor nerve is available. It is preferred that the donor nerve innervates muscles that have synergistic movements to the injured muscle to aid in cortical plasticity. In contrast, a “babysitting” nerve transfer sacrifices a donor nerve and uses the donor axons to occupy the target muscle, maintaining its health while the injured nerve regenerates. After a sufficient recovery period, there is a second procedure in which the donor nerve is removed, and the regenerated injured nerve is ligated. However, a common limitation is the lack of available donor nerves, especially in more severe injury cases, such as brachial plexus or spinal cord injuries. Therefore, an alternative approach is needed.
The transplantation of human induced pluripotent stem cell (iPSC) derived spinal motor neurons (SMNs) to a rodent nerve injury model has shown initial success but requires functional improvement to hold potential for a cell therapy. For enhanced axonal growth and muscle innervation, we hypothesized that *in vitro* human iPSC derived motor neuron embryoid bodies (EBs), which are three dimensional cell clusters that contain post-mitotic motor neurons, progenitor neurons, and glial cells, injected *in vivo* could “babysit” muscle in a rat sciatic nerve injury model. Motor neurons from the EBs would occupy the NMJs within the target muscles and maintain muscle mass and function. Using a small molecule differentiation protocol, we generated human iPSC-derived, tdTomato-tagged EBs. EBs were injected into the distal portion of a transected sciatic nerve, specifically the tibial fascicle. Transplanted cell survival, axon growth, and functional innervation of the target muscles were analyzed 4-6 months post-transplantation. We found robust survival of transplanted cells and axonal growth towards the distal tissue. Through immunofluorescence analysis, we characterized neuronal, motor neuron, pluripotency markers, as well as the presence of NMJs in injured muscle. Based on these findings, we find this intervention promising and in need of further investigation.

Disclosures: **A. Mistry:** None. **L. Capano:** None. **A.H. Held:** None. **B. Wainger:** 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.; Funding from Argenx. F. Consulting Fees (e.g., advisory boards); Scientific Advisory Board for Quralis.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.17/D37

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CIHR f18- 01234

Title: Locomotor and cognitive deficits observed in older mice with inhibited remyelination following spinal cord injury

Authors: *S. M. WHEELER[1], B. R. KONDILES[2], S. B. MANESH[1], J. LIU[1], M. LU[3], W. TETZLAFF[4];
[1]Univ. of British Columbia, Vancouver, BC, Canada; [2]Intl. Collaboration on Repair Discoveries, Vancouver, BC, Canada; [3]Icord, Vancouver, BC, Canada; [4]ICORD, Univ. of British Columbia - ICORD, Vancouver, BC, Canada

Abstract: The average age of spinal cord injury (SCI) continues to increase reflecting the aging population; in Canada now being 54.3 years, compared to 28.6 years in the 1970s. SCIs impact multiple functions of the body including motor, autonomic, and cognitive functions; we have limited understanding of the mechanisms responsible for the less favourable outcomes of SCI at higher ages. Following the initial impact of SCI, a secondary injury cascade begins, leading to apoptosis of oligodendrocytes and focal demyelination of spared axons near the injury site followed by remyelination in younger animals. Surprisingly, when remyelination was inhibited in young adult mice no differences in locomotor recovery post SCI were observed (Duncan et al. 2018, Nat. Comm. PMID: 30076300). To explore the importance of age and remyelination we compared the functional recovery of young adult (3-5 month) to older (15-18 month) transgenic mice of both sexes following either a 70kDyne thoracic level 9 contusion or a sham injury (laminectomy). We targeted a key transcription factor for myelination expressed in oligodendrocyte progenitor cells (OPCs) known as Myrf, by using a transgenic mouse with exon 8 of the Myrf gene floxed ($Myrf^{fl/fl}$). This was crossed with a PDGFRαCreERT2 driver line mouse, so upon tamoxifen administration, we could conditionally prevent OPC maturation into oligodendrocytes (OL). Thereby inhibiting new myelination. Mice were compared to littermate controls, carrying a functional *Myrf* gene. We found that injured, older, and remyelination incompetent mice displayed delayed/impaired locomotor recovery, as assessed through the Basso Mouse Scale, horizontal ladder, and Noldus Catwalk. Cognitive deficits were observed in the Y-maze and the object relocation task. No changes were observed in terms of anxiety or depression-like behaviors, examined via the marble burying task, the elevated plus maze, marble burying task, fecal boli counts, or three chamber social test. Ongoing histology aims to determine how age and remyelination inhibition impact the myelin near the lesion, OPC and OL density, as well as the amount of spared tissue 3 months post injury. Our current results indicate that remyelination treatments may have a greater impact in older individuals with SCI compared to younger ones, suggesting a need for personalized therapies post SCI. Funded by CIHR.

Disclosures: S.M. Wheeler: None. **B.R. Kondiles:** None. **S.B. Manesh:** None. **J. Liu:** None. **M. Lu:** None. **W. Tetzlaff:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.18/D38

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CONAHCyT del proyecto CF1311312 de DLCQ

Title: Plasma-synthesized polypyrrole treatment: effect on unilateral six lumbar avulsion in the female rabbit

Authors: Z. FLORES LOZADA[1], A. FLORES HERNANDEZ[1], J. MORALES-MEDINA[2], J. MORALES CORONA[3], I. JIMÉNEZ ESTRADA[4], Z. Z. RENE[5], *D. CORONA QUINTANILLA[1];
[1]Univ. Autónoma de Tlaxcala, Tlaxcala, Mexico; [2]Ctr. de Investigación y Estudios Avanzados, Tlaxcala, Mexico; [3]Dept. de Física, Univ. Autónoma Metropolitana Iztapalapa, México, Mexico; [4]Fisiología, Biofísica y Neurociencias, Cinvestav, México, Mexico; [5]CTBC, Univ. Autónoma de Tlaxcala, Tlaxcala, Mexico

Abstract: The rupture or avulsion of the six lumbar ventral root (L6 VRA) produces a decrease in nerve fibers that reduces the information transmitted through the nerve, due to the axonal damage caused and the restoration of motor functions is minimal without some nerve repair strategy. . Given the complex pathophysiology of L6 VRA, there are no therapeutic strategies that have been completely effective and compatible in restoring lost functions. Currently, the use of biopolymers has gained relevance to treat injuries of the nervous system, including polymers compatible with the nervous system and conductors of electricity, such as polypyrrole (PPy). The objective of this project is to determine if the PPy implant recovers the characteristics of locomotion and the compound action potential (CAP) of peripheral nerves in the rabbit. For this study, Chinchilla rabbits of 8 ± 2 months of age were used, divided into 3 groups (n=5): a) Sham, b) L6 VRA and c) L6 VRA +PPy. The animals were anesthetized with isoflurane and underwent right unilateral avulsion surgery; after three days of recovery, a 30-minute behavioral observation was carried out on days 4, 15 and 29 post-injury. Thirty days later, the rabbits were anesthetized with urethane, the femoral and peroneal nerves were located, dissected and placed on suction electrodes, to record the PAC of each nerve in vitro. The results indicate that L6 VRA causes important changes in posture, causing paralysis and deviation of the right lower limb. Likewise, it modifies the parameters of the PAC, by decreasing the amplitude and duration. Meanwhile, PPy implantation after L6 VRA promotes the recovery of locomotion and maintains nerve conduction. PPY implantation in injuries such as L6 VRA recovers and reestablishes the functions of the femoral and peroneal nerves.

Disclosures: Z. Flores Lozada: None. **A. Flores Hernandez:** None. **J. Morales-Medina:** None. **J. Morales Corona:** None. **I. Jiménez Estrada:** None. **Z.Z. Rene:** None. **D. Corona Quintanilla:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.19/D39

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation Grant #1000927

Title: The impact of concurrent neural injuries on secondary tissue loss and behavioral function in rats

Authors: *A. TREVINO, K. N. COLPITTS, A. AWALT, V. BALENTINE, J. W. GRAU; Texas A&M Univ., College Station, TX

Abstract: Our laboratory has previously shown that pain (nociceptive) stimulation after a spinal cord injury leads to the expansion of hemorrhage and undermines locomotor recovery (Turtle, 2019, *Exp Neurol*, *311*, 115). Noxious stimulation also increases the area of hemorrhage after a traumatic brain injury (TBI; Bean, 2019, *J Neurotrauma, 36,* A-72). These observations are important because neural injuries are often accompanied by other tissue damage (polytrauma), which can fuel secondary tissue loss. The current study examined whether concurrent neural injuries (SCI+TBI) amplify tissue loss and the impairment in motor function. Thirty-two male Sprague-Dawley rats received a moderate TBI or sham craniectomy surgery plus a moderate T12 contusion injury or sham laminectomy only surgery, with surgery order counter balanced across conditions. A controlled cortical impact device over the right parietal lobe was utilized for the TBI procedures (2mm impactor tip, 4m/s, and 3mm deformation). A MASCIS device was used for the contusion injury at the level of T11-T12 vertebrae (10g impactor tip, height of 12.5mm). A day after the surgical procedures hindlimb locomotor function was assessed. Rats were perfused and the brain and a 1-cm region of the spinal cord that encompassed the site of injury were collected to assess the extent of hemorrhage. Brain and spinal cord tissue were sectioned and stained with hematoxylin and eosin (H&E), and imaged to analyze hemorrhage. In the groups that had concurrent injuries, TBI did not appear to amplify the disruption in locomotor function. Likewise, a concurrent SCI had minimal impact on the extent of hemorrhage after TBI. We are currently assessing whether the sham surgery, per se, had an adverse effect.

Disclosures: A. Trevino: None. **K.N. Colpitts:** None. **A. Awalt:** None. **V. Balentine:** None. **J.W. Grau:** None.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.20/Web Only

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 5R21NS119732-02

Title: Modulating NeuroD1 Expression Levels by Using miR-124 to Improve Neuronal Reprogramming

Authors: *N. N. MSEIS-JACKSON[1], M. JIANG[2], X. CHEN[3], M. SHARMA[4], C. WILLIAMS[2], H. LI[5];
[1]Neurosci. and Regenerative Med. Program, Med. Col. of Georgia at Augusta Univ., Augusta, GA; [2]Med. Col. of Georgia at Augusta Univ., Augusta, GA; [3]Neurosci. & Regenerative Med.

Program, Med. Col. of Georgia at Augusta Univ., Augusta, GA; [4]Med. Col. of George at Augusta Univ., Augusta, GA; [5]Neurosci. & Regenerative Med., Med. Col. of Georgia at Augusta Univ., Augusta, GA

Abstract: Spinal cord injury (SCI) is a devastating central nervous system (CNS) injury that adversely impacts health and quality of life. This injury activates a cascade of events that results in the formation of glial scarring and neuronal loss, leading to a major impairment of sensory and motor function. A healthy spinal cord contains heterogeneous spinal neurons, such as motor neurons, sensory neurons, inhibitory neurons, and excitatory interneurons. Evidently, after SCI, there is a deprivation of different interneuron subtypes. Astrocyte-to-neuron reprogramming presents a promising treatment for patients with spinal cord injury (SCI). NeuroD1 (ND1) transcription factor can convert reactive astrocytes into neurons directly to replenish lost neurons, which is a primary objective in treating SCI. Persistent overexpression of ND1 generates primarily glutamatergic neurons. However, diversified neuronal subtypes are needed to ensure adequate neuronal connectivity after SCI. Therefore, we created a novel construct that integrates ND1 expression with a microRNA (miRNA) binding site (miR-124b) in our neuronal reprogramming system. MiR-124 is neuronal-specific and one of the most expressed miRNAs in neurons. This construct will still achieve a high ND1 expression level in astrocytes for reprogramming. Once reprogrammed neurons are generated, there will be a rise in the level of endogenous miR-124, which will bind to its specific binding site within the construct, inhibiting ND1 expression. We propose that a lower level of ND1 after neuronal reprogramming could facilitate the development of various subtypes of neurons, including both excitatory and inhibitory ones. We have characterized the dynamic expression pattern of ND1 and the neuronal reprogramming capacity of this novel construct aiming to improve neuronal reprogramming outcomes.

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Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.21/D40

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Dana & Albert R. Broccoli Charitable Foundation

Title: Global behavior and physiological transformation one decade after spinal cord injury plus unilateral brachial plexus avulsion.

Authors: *K. KIJIMA[1,2], I. MONTOYA[5], H. R. TORRES SOLANO[3], H. ZHONG[4], V. EDGERTON[6];
[1]Dept. of Orthopedic Surgery, Kyushu Univ., Beppu Shi, Oita Ken, Japan; [2]Rancho Res. Inst.,

Los Angeles, CA; [3]Rancho Res. Inst., Rancho Res. Inst., MARINA DEL REY, CA; [4]Rancho Res. Inst., Rancho Res. Inst., Downey, CA; [5]Rancho Res. Inst., California State University, Los Angeles, Los Angeles, CA; [6]Dept of Neurolog. Surgery and Neurorestoration Ctr., Univ. of Southern California, Keck Sch. of Medicine, Neurorestoration Ctr., Los Angeles, CA

Abstract: Electrical transcutaneous spinal neuromodulation can generate a very wide range of physiological states of spinal and supraspinal networks at levels of stimulation well below motor threshold. The combination of Noninvasive transcutaneous spinal electrical stimulation (NTES) and activity-based neurorehabilitation therapy (ABNT) can facilitate the reorganization of preserved neural circuits to a higher state of functional connectivity within and among multiple spinal segment levels and supraspinal networks. Given the evidence of multiple functional reorganization strategies of neural networks reported in animal models within and among spinal and supraspinal networks in facilitating motor recovery, we hypothesized that similar recovery strategies can be facilitated in a human, 11 years post-SCI (unilateral brachial avulsion plus bilaterally complete thoracic injury) when intermediately treated 2-3/week over a period of 3 years with NTES neuromodulation combined with ABNT. After 3 years of treatment intervention, the AIS grade improved from A to C, and the patient's walking ability with Ekso, an exoskeletal technology that assists walking, also improved. When the short-term effects of ABNT and NTES were examined, it was clear that walking ability improved within a single rehabilitation session, suggesting that ABNT and NTES may promote neural plasticity and re-educate the nervous system in a short period of time. Furthermore, long-term ABNT and NTES improved neurological function by causing a reorganization of novel functional connections within and among descending and ascending neural and propriospinal networks, including a concomitant reorganization of brain function. In summary, the combination of NTES and ABNT has the potential to facilitate the reorganization of residual supraspinal-propriospinal and spinal networks years after injury with the likelihood of activity-dependent mechanism playing an important role in guiding the reorganization newly developed networks toward higher functionality.

Disclosures: K. Kijima: None. **I. Montoya:** None. **H.R. Torres Solano:** None. **H. Zhong:** None. **V. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ONWARD, SpineX.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.22/D41

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Founding: Dana & Albert R. Broccoli Charitable Foundation

Title: Transcutaneous spinal neuromodulation facilitates lower limb activation 11 years after a complete, complex, paraplegic spinal injury

Authors: *J. B. RICHTER[1], C. JOHNSON[1], H. ZHONG[1], I. MONTOYA[2,3], K. KIJIMA[4], V. EDGERTON[5,3];
[1]Rancho Res. Inst., Downey, CA; [2]California State Univ., Los Angeles, Los Angeles, CA; [3]Rancho Research Institute, Downey, CA; [4]Kyushu Univ., Beppu Shi, Oita Ken, Japan; [5]Dept Integrative Biol. & Physiol., Univ. of Southern California, Keck Sch. of Med., Neurorestoration Ctr., Los Angeles, CA

Abstract: In uninjured humans, the motor output of the lower limbs can be amplified by simultaneously activating the upper limbs. We hypothesized that this phenomenon could be useful after paraplegia and could become even greater when combined with electrical transcutaneous spinal cord stimulation (tSCS). We also examined the latency of voluntary activation and suppression after paraplegia. tSCS consisted of electrodes placed at T11/L1 to apply tonic biphasic 20 mA and 50 mA stimuli in a subject 11 years post-SCI (bilaterally complete thoracic injury plus a unilateral brachial avulsion). EMG sensors (Biometrics Ltd DataLITE) were placed on the right and left rectus femoris, hamstrings, tibialis anterior, and soleus, recording at 2000 Hz. Exercises were conducted on a NuStep device that enables generation of rhythmic, bilateral arm-leg flexion and extension with no weight bearing via the lower limbs. An alternating series of about 10 cycles, beginning with the subject exerting the necessary effort to mimic a cadence of 27.5 cycles/min was performed with the combined effort of all four limbs (active)—then immediately after, the subject continued lower limb activation but without the effort of upper limbs (cadence was maintained externally by lab assistant). Finally, the initial active phase was repeated. EMG data were processed with MATLAB and filtered using an ACSR filter with a window length of 400 ms followed by a 4th order, 6 Hz, Butterworth filter. The highest muscle activation in the lower limbs occurred during the first combined leg plus arm active phase and was largely reduced during the arm passive phase. The EMG activity of the lower limbs during the second active phase failed to reach the levels of the first active phase of arms and legs, but tonic biphasic 20 mA neuromodulation partially mitigated this loss of activity. tSCS also shortened the latency of muscle activation in the first active phase. These findings suggest that simultaneously engaging the upper limbs when attempting activation of the lower limbs, can amplify levels of activation of lower limbs after a severe paraplegic injury and this effect can be further amplified with tSCS.

Disclosures: J.B. Richter: None. **C. Johnson:** None. **H. Zhong:** None. **I. Montoya:** None. **K. Kijima:** None. **V. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ONWARD, SpineX.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.23/D42

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Dana & Albert R. Broccoli Charitable Foundation

Title: Optimizing Ekso Training Combined with Non-invasive Transcutaneous Spinal Stimulation in Complete Spinal Cord Injury Patient

Authors: *H. ZHONG[1], C. JOHNSON[2], K. KIJIMA[3], H. TORRES SOLANO[2], J. RICHTER[4], I. MONTOYA[4], V. EDGERTON[5,6];
[1]Rancho Los Amigos Natl. Rehabil. Ctr., Downey, CA; [2]Rancho Res. Inst., Rancho Los Amigos Natl. Rehabil. Ctr., Downey, CA; [3]Kyushu Univ., Beppu Shi, Oita Ken, Japan; [4]Rancho Res. Inst., Downey, CA; [5]Dept of Neurolog. Surgery and Neurorestoration Ctr., Univ. of Southern California, Keck Sch. of Med., Neurorestoration Ctr., Los Angeles, CA; [6]Rancho Research Institute, Downey, CA

Abstract: The integration of non-invasive transcutaneous spinal cord stimulation (tSCS) with activity-based neurorehabilitation therapy (ABNT) has demonstrated significant improvements in multisystem functions among individuals with chronic spinal cord injury. The Exoskeleton (Ekso Bionics) offers weight-bearing stepping capabilities to those with complete spinal cord injury, providing varying degrees of mechanical assistance when combined with subject-specific adaptive parameters. Here, we studied a participant with a T4/T5 complete spinal cord injury and right-side brachial avulsion from 9 to over 11 years post-injury. The participant has undergone Ekso training paired with tSCS sessions 2-3 times per week, each lasting approximately 60 minutes. Spinal neuromodulation was targeted at the T11 and L1 spinal levels using predominantly biphasic stimulation at 20 or 50 mA (SpineX SCON). The assistance level from the Ekso robot gradually decreased from 100% to 60%. Initially, the ProStep assistant mode was employed, then it was transitioned to ProStep+ mode. After successful training at a 70% assistance from the robot, swing time during waking occurred with consistent right and left leg symmetry even without tSCS. Yet, as the assistance level decreased to 65%, swing time increased on the left side compared to the right. When tSCS at 20mA was used, however, similar symmetrical stepping was observed. Decreasing the assistance level generally led to shortened step lengths, except when transitioning from 65% to 60%, where 50mA tSCS maintained step length. Newly emerged functional spinal-supraspinal bidirectional connectivity facilitated recovery of functionally relevant proprioception of foot placement and improvements of locomotion as the level of robotic assistance was progressively reduced, involving bidirectional spinal-supraspinal neurocircuitry reorganization. In optimizing these adaptive events, it was crucial to identify subject-specific combinations of interventional parameters encompassing level of robotic assistance, site and intensity of neuromodulation, and training duration. Moreover, the data underscores the interdependence between robotic assistance level and learning efficacy at specific neuromodulation currents and how these variables change interdependently with improved performance. These results further illustrate the persistence of the adaptive potential for years post-spinal injury.

Disclosures: H. Zhong: None. **C. Johnson:** None. **K. Kijima:** None. **H. Torres Solano:** None. **J. Richter:** None. **I. Montoya:** None. **V. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Part ownership of ONWARD and SpineX Inc...

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.24/D43

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Dana & Albert R. Broccoli Charitable Foundation

Title: Reduction of exoskeleton robotic assistance and increased intensity of transcutaneous spinal neuromodulation changes EMG activity after a complete spinal injury

Authors: *C. JOHNSON[1,2], H. ZHONG[3], J. RICHTER[1], I. MONTOYA[4], H. R. TORRES SOLANO[5], K. KIJIMA[6], V. EDGERTON[7];
[1]Rancho Res. Inst., Downey, CA; [2]Rancho Research Institute, Rancho Los Amigos National Rehabilitation Center, Downey, CA; [3]Rancho Res. Inst., Rancho Los Amigos Natl. Rehabil. Ctr., Downey, CA; [4]Rancho Res. Inst., California State Univ., Los Angeles, Los Angeles, CA; [5]Rancho Res. Inst., Rancho Res. Inst., MARINA DEL REY, CA; [6]Kyushu Univ., Beppu Shi, Oita Ken, Japan; [7]Dept Integrative Biol. & Physiol., Univ. of Southern California, Keck Sch. of Med., Neurorestoration Ctr., Los Angeles, CA

Abstract: Exoskeleton robotic devices are used in rehabilitation practices to assist physical therapy of individuals with neurological disorders to provide patients with some degree of locomotion, as they can provide new possibilities for severely paralyzed patients to walk. Experiments from multiple laboratories using a noninvasive, transcutaneous strategy to neuromodulate the spinal cord have consistently demonstrated that individuals diagnosed clinically as having a complete spinal cord injury can regain functionally novel connectivity that enables voluntary motor control. The combinational pairing of these technologies may enhance neural plasticity. However, it is unclear how changes in the parameters of each system, assistance level and transcutaneous stimulation intensity, affect plasticity of neuronal networks. Here we used an exoskeleton (Ekso Bionics NR) and non-invasive electrical spinal neuromodulation in a single spinal cord injured subject, who is 11 years post-injury and suffers from a unilateral brachial plexus nerve root avulsion injury and a thoracic spinal cord injury at the T4/T5 level, to provide clarity. The subject of this case study performed multiple trials of walking on a flat surface with different assistance levels, 90% to 55%, assistance under 3 different stimulation parameters, no stimulation, 20mA biphasic, and 50mA biphasic across 3 days. Electromyography (EMG) recordings were taken from the proximal (hamstrings, rectus femoris) and distal (tibialis anterior and soleus) muscles for the left and right side. We full wave rectified and filtered EMG data and divided it into gait cycles using signals from left and right accelerometers (heel strike to the next heel strike). The mean RMS across all gait cycles in each condition was averaged for each muscle, then averaged across all muscle resulting in a single value for muscle activity for each assistance level and stimulation level. We found at lower assistance levels average EMG activity using 50mA biphasic was greater compared to no stimulation and 20mA biphasic. Also, stimulating at 50mA biphasic reduced variability in muscle activity, suggesting activity produced during walking is consistent. Interestingly, at higher levels of assistance, greater stimulation, 50 mA biphasic reduced the average muscle

activity compared to no stimulation. These results suggest that at lower assistance levels with increased spinal stimulation, may allow for better gait mechanics, but may hinder muscle activity with higher assistance levels.

Disclosures: C. Johnson: None. **H. Zhong:** None. **J. Richter:** None. **I. Montoya:** None. **H.R. Torres Solano:** None. **K. Kijima:** None. **V. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ONEARD, SpineX.

Poster

PSTR021: Spinal Cord Injury: Recovery

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.25/D44

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Developmental pyrethroid exposure disrupts molecular pathways for MAP kinase and circadian rhythms in mouse brain

Authors: J. NGUYEN[1], M. A. CURTIS[2], A. S. IMAMI[3], W. RYAN[4], R. SHUKLA[5], *R. MCCULLUMSMITH[1], G. W. MILLER[6], J. P. BURKETT[7];
[1]Univ. of Toledo, Toledo, OH; [2]Neurosci. & Neurolog. Disorders, Univ. of Toledo Col. of Med. Neurosci. & Neurolog. Disorders, Toledo, OH; [3]Univ. of Toledo Col. of Med. Neurosci. & Neurolog. Disorders, Toledo, OH; [4]Bioinformatics, Univ. of Toledo, Toledo, OH; [5]Neurobio. of Aging and Depression, Univ. of Wyoming, Toronto, ON, Canada; [6]Ctr. for Neurodegenerative Dis., Emory Univ., Atlanta, GA; [7]Neurosciences, Univ. of Toledo, Toledo, OH

Abstract: Neurodevelopmental disorders (NDDs) are a category of pervasive disorders of the developing nervous system with few or no recognized biomarkers. A significant portion of the risk for NDDs, including attention deficit hyperactivity disorder (ADHD), is contributed by the environment, and exposure to pyrethroid pesticides during pregnancy has been identified as a potential risk factor for NDD in the unborn child. We recently showed that low-dose developmental exposure to the pyrethroid pesticide deltamethrin in mice causes male-biased changes to ADHD- and NDD-relevant behaviors as well as the striatal dopamine system. Here, we used an integrated multiomics approach to determine the broadest possible set of biological changes in the mouse brain caused by developmental pyrethroid exposure (DPE). Using a litter-based, split-sample design, we exposed mouse dams during pregnancy and lactation to deltamethrin (3 mg/kg or vehicle every 3 days) at a concentration well below the EPA-determined benchmark dose used for regulatory guidance. We raised male offspring to adulthood, euthanized them, and pulverized and divided whole brain samples for split-sample transcriptomics, kinomics and multiomics integration. Transcriptome analysis revealed alterations to multiple canonical clock genes, and kinome analysis revealed changes in the activity of multiple kinases involved in synaptic plasticity. Multi-omic integration revealed a dysregulated protein-protein interaction network containing primary clusters for mitogen-

activated protein (MAP) kinase cascades, regulation of apoptosis, and synaptic function. These results demonstrate that DPE causes a multi-modal bio-phenotype in the brain relevant to ADHD and identifies new potential mechanisms of action.

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Poster

PSTR022: Opioids

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.01/D45

Topic: D.01. Somatosensation – Pain and Itch

Support: 2021ZD0203302

Title: Spinal mechanisms underlying opioid-induced mechanical hypersensitivity and tolerance

Authors: ***G. YIN**[1], *G. YIN[1], D. DONG[1], F. DU[1], X. LIU[2], J. HUO[1], L. CHENG[3]; [1]Southern Univ. of Sci. and Technol., Shenzhen, China; [2]Southern Univ. of Sci. and Technol., shenzhen, China; [3]Dept. of Biol., Southern Univ. of Sci. and Technol., Shenzhen, China

Abstract: Repeatedly administration of opioid drugs is associated with two major side effects: opioid-induced hypersensitivity (OIH) and analgesic tolerance. Among different forms of OIH and tolerance, the opioid receptors and cell types mediating mechanical OIH and analgesic tolerance remain unresolved. According to our recent study, peripheral μ-opioid receptors (MORs) or MOR-expressing neurons are required for the development of morphine-induced thermal, but not mechanical OIH and tolerance, suggesting modality-specific mechanisms underlying OIH and tolerance. Here we reported that the kappa opioid receptors (KORs) in the spinal dorsal horn control morphine-induced mechanical OIH and tolerance (but not thermal tolerance) via modulating the excitability of KOR-expressing neurons. Conditional knockout of KORs from dorsal horn neurons (n = 5-9 mice per group; both male and female were included in this study), or intersectional genetic ablation of dorsal horn KOR-expressing neurons (n = 7-9 mice per group), prevented the development of 5-day morphine-induced mechanical, but not thermal OIH and tolerance. Moreover, we found that 5-day morphine dramatically increased the excitability of dorsal horn KOR-expressing neurons, and chemogenetic silencing (n = 6 mice per group) these neurons could prevent/rescue morphine mechanical OIH and/or tolerance. Conversely, chemogenetic activation of KOR-expressing dorsal horn neurons re-occurred morphine mechanical OIH (n = 6 mice per group), and caused a transition from morphine-sensitive to morphine-resistant state under neuropathic pain condition (n = 5-7 mice per group). Collectively, our data suggest that dorsal horn KORs could control morphine-induced mechanical forms of OIH and tolerance via modulating the excitability of dorsal horn KOR-expressing neurons. Targeting dorsal horn KORs/KOR-expressing neurons, could therefore

provide preclinical studies and/or clinical trials a mechanism-based, modality-specific strategy to resolve opioid-induced mechanical forms of OIH and analgesic tolerance.

Disclosures: G. Yin: None. **G. Yin:** None. **D. Dong:** None. **F. Du:** None. **X. Liu:** None. **J. Huo:** None. **L. Cheng:** None.

Poster

PSTR022: Opioids

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.02/D46

Topic: D.01. Somatosensation – Pain and Itch

Support: R34NS121875
R01DA023281

Title: Identifying brain regions involved in chronic-pain processing and analgesic treatment

Authors: *M. MARTINEZ[1], A. OZAWA[2], L. TOLL[2];
[1]Stiles-Nicholson Brain Inst., Florida Atlantic Univ., Jupiter, FL; [2]Biomed. Sci., Florida Atlantic Univ., Jupiter, FL

Abstract: Those who suffer from chronic neuropathic pain have a significantly decreased quality of life, and many rely on the treatment of opioids for survival. Although our understanding of the sensory pain pathway from peripheral nerves to the brain is well-established, the neural circuitry and cellular components underlying pain perception within the brain have not been investigated as thoroughly. In this study, we employed a genetically engineered mouse model and a brain tissue “clearing” technique to identify specific neuronal populations, throughout the brain, that are activated during chronic neuropathic pain. By visualizing these neurons in three-dimensional space, we were able to analyze their spatial density and distribution, thereby identifying regions containing chronic pain-dependent activated cells in specific brain regions. Furthermore, we investigated the brain regions that were activated by the administration of a mu-opioid receptor agonist, morphine and a NOP receptor agonist, Ro 64-6198 in order to obtain a better understanding of the analgesic actions mediated by these opiates in the brain under a chronic pain condition. We observed a difference in the number of activated cells in regions important for nociceptive processing. Additionally, we found a change in the patterns of activation elicited by analgesic treatment. Our findings will allow us to understand the regulatory mechanism underlying pain-related behaviors and analgesic function produced by opiates by elucidating the brain regions in which cells are selectively activated during chronic pain or analgesic treatment. This knowledge may aid in the advancement of understanding where chronic pain and pain relief are happening in the brain and contribute to the development of targeted pain therapies to alleviate its debilitating effects.

Disclosures: M. Martinez: None. **A. Ozawa:** None. **L. Toll:** None.

Poster

PSTR022: Opioids

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.03/D47

Topic: D.01. Somatosensation – Pain and Itch

Title: The expression of μ-opioid receptor on spinal neuropeptide y-positive neurons negatively regulates the analgesic effect of morphine

Authors: *Y. WU[1], Q. ZENG[1], Z. WANG[2];
[1]Southern Univ. of Sci. and Technol., Shenzhen, China; [2]Sch. of Med., Southern Univ. of Sci. and Technol., Shenzhen, China

Abstract: Pain, although not directly life-threatening, profoundly diminishes patients' quality of life. Despite the availability of various pain management medications, opioids remain indispensable, although they have associated side effects. As an inhibitory G protein-coupled receptor, activated mu-opioid receptors (MORs) suppress neuronal excitability, thereby achieving analgesia. However, spinal dorsal horn opioid receptors are co-expressed with both excitatory and inhibitory neurons. Therefore, this study investigated the regulatory role of the MOR expressed on a large class of inhibitory neurons (NPY^+ neurons) in the spinal dorsal horn on the analgesic effects of opioids. We employed in situ hybridization to examine NPY system and MOR expression patterns in the spinal dorsal horn, revealing that approximately 38.14% of neurons expressing *Oprm1* mRNA also expressed *Npy* mRNA, and 40.19% expressed *Npy1r* mRNA. Moreover, within Npy^+ neurons and $Npy1r^+$ neurons, 33.71% and 21.13% co-expressed *Oprm1*, respectively. Additionally, we employed chemical genetics to reveal that chemogenetic activation of NPY-positive neurons in the spinal cord significantly attenuates acute and chronic inflammatory pain induced by formalin and CFA, while their inhibition led to pronounced pain-like behaviors in mice. Through electrophysiological recordings, we discovered that morphine can induce outward currents in NPY-positive neurons in the spinal dorsal horn, further elucidating the inhibitory effect of intrathecal morphine on NPY^+ neurons. We further investigated WT mice by co-administering NPY and morphine intrathecally to examine whether exogenous supplementation of NPY could potentiate the analgesic effect weakened by the decreased release of NPY due to the inhibition of NPY neurons by morphine. We found synergistic analgesic effects of NPY and morphine in both acute and chronic inflammatory pain models. Conditional knockout of MOR receptors in NPY-positive neurons significantly enhanced morphine's analgesic effect under chronic pain conditions induced by CFA. Finally, enhanced excitability of NPY-positive neurons in lumbar spinal cord slices of Npy^{Cre}; Ai9 mice in the chronic inflammatory pain model was detected using electrophysiological techniques. We conclude that both the NPY system and the opioid system in the spinal dorsal horn participate in the transmission of pain signals. Specifically, the expression of MOR on NPY-positive neurons exerts a negative regulatory role in opioid analgesia, while NPY1R-positive neurons may mediate the synergistic enhancement of opioid drugs by NPY in both acute and chronic inflammatory pain.

Disclosures: **Y. Wu:** None. **Q. Zeng:** None. **Z. Wang:** None.

Poster

PSTR022: Opioids

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.04/D48

Topic: D.01. Somatosensation – Pain and Itch

Title: Analysis of Endomorphin Analogues as Candidate Drugs for Pain Relief

Authors: ***C. OGBU**[1], M. J. BARTLETT[2], L. SZABO[1], T. FALK[3], R. POLT[4], M. L. HEIEN[1]; [1]Chem. and Biochem., Univ. of Arizona, Tucson, AZ; [2]Dept. of Neurol., Col. of Med., Tucson, AZ; [3]Dept. Of Neurol., Univ. of Arizona, Tucson, AZ; [4]Chem. & Biochem., The Univ. of Arizona, Tucson, AZ

Abstract: Although neuropeptide-based drugs have garnered widespread attention due to their high efficacy and good selectivity, they are susceptible to enzymatic degradation, which leads to low blood-brain barrier (BBB) penetration and a short half-life. Previous studies have shown that glycosylation of neuropeptides increases their blood-brain barrier penetration and stability. Endomorphins are endogenous opioid peptides that have potential as analgesics and as a morphine substitute due to their selectivity and affinity for the μ-opioid receptor. Introducing a lactam bridge and glycosylation of the native endomorphin increases BBB penetration, making it a potent antinociceptive opioid agonist. These analogues of endomorphin have demonstrated comparable or superior antinociceptive efficacy to morphine while reducing multiple adverse effects, including abuse potential, tolerance, respiratory depression, and inflammatory glial responses. Here, we studied the *In Vivo* blood-brain barrier penetration and pharmacokinetics of two endomorphin analogues, glycosylated (A1 Glc) and unglycosylated (ZH853) analogues administered via lateral tail vein in male rats. Blood was sampled via carotid artery catheterization, and brain dialysate was sampled via microdialysis of the rat striatum at different time points. Plasma and cerebrospinal fluid drug concentrations were determined using liquid chromatography-tandem mass spectrometry. Preliminary results show that A1 Glc has an ~8-fold increase over ZH853 in the cerebrospinal fluid (CSF) and a ~1.5-fold increase over ZH853 in the plasma. A1 Glc showed a plasma drug area under the curve (AUC_{0-t}) of 196.0 ± 52.8 μM*minutes, a CSF drug AUC_{0-t} of 168.0 ± 85.1 μM*minutes (mean ± SEM, n = 3). ZH853 showed a plasma drug area under the curve (AUC_{0-t}) of 134.1 ± 34.2 μM*minutes (n = 3), a CSF drug AUC_{0-t} of 21.1 ± 3.3 μM*minutes (n = 2). The unglycosylated peptide diffuses through the BBB at lower levels and at a time frame different (CSF T_{max} = 25 minutes) from the glycoside, which penetrates the BBB almost immediately (CSF T_{max} = 5 minutes). These cyclic glycosylated neuropeptides have the potential as analgesic and as a treatment for opioid use disorder.

Disclosures: **C. Ogbu:** None. **M.J. Bartlett:** None. **L. Szabo:** None. **T. Falk:** None. **R. Polt:** None. **M.L. Heien:** None.

Poster

PSTR022: Opioids

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.05/D49

Topic: D.01. Somatosensation – Pain and Itch

Title: Differential opioid receptor expression in mouse dorsal root ganglia

Authors: *M. GERON[1], A. TASSOU[1], J. NIEHAUS[1], H. ZENG[2], G. SCHERRER[1];
[1]Neurosci. Ctr., Dept of Cell Biol. and Physiol., The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Allen Inst. for Brain Sci., Seattle, WA

Abstract: While opioids are recognized as potent analgesics, opioid receptor activation throughout the brain produces harmful side effects and prompts the need for safer analgesic strategies. One promising approach is to selectively target opioid receptors in dorsal root ganglion (DRG) neurons. To accomplish this, it is essential to determine the DRG neuron types that express opioid receptors (MOR, DOR, KOR encoded by *Oprm1*, *Oprd1*, *Oprk1*), the tissues these neurons innervate, and the pain modalities they mediate. To fill these gaps in knowledge, we employed transcriptomic and histological techniques, and novel knock-in mouse lines expressing DNA recombinases in opioid receptor-expressing cells. Leveraging single-cell RNA sequencing and identified marker genes for DRG neuron-types, we found that *Oprm1* is broadly expressed by multiple types of peptidergic nociceptors and pruriceptors. These neurons include nociceptors that respond to thermal or mechanical stimuli, innervate visceral organs or skin, and form peripheral free nerve endings or specialized sensory structures. In contrast, *Oprd1* and *Oprk1* are confined to specific clusters; while both receptors are expressed by Aβ-low threshold mechanoreceptors (LTMRs) that detect innocuous mechanical stimuli, they are differentially expressed by C-type neurons that are either mostly peptidergic (*Oprk1*) or non-peptidergic (*Oprd1*), some coexpressing *Oprm1*. To validate and extend on these findings, we labeled opioid receptor-expressing neurons' somata and axons in *Oprm1*^{Cre}, *Oprd1*^{Cre}, *Oprk1*^{Cre}, *Oprd1*^{Cre}::*Oprm1*^{Flp}, or *Oprk1*^{Cre}::*Oprm1*^{Flp} mice by injecting viruses expressing fluorophores in a Cre- and/or Flp-dependent manner. We found that neurons coexpressing either DOR+ and MOR+ or KOR+ and MOR+ represent a small fraction of DRG neurons and are mostly peptidergic. MOR+ neurons project to the superficial laminae of the spinal cord dorsal horn, consistent with MOR expression in nociceptors, whereas DOR+ and KOR+ neurons mainly project to the deeper dorsal horn laminae and to the brainstem dorsal column nuclei that process innocuous mechanical stimuli. Imaging of nerve endings in whole-mount cleared tissues showed that in skin DOR and KOR are present in different types of Aβ-LTMRs since Aβ-Field- and SA-LTMRs are DOR+, and RA-LTMRs are mainly KOR+. In the bladder and colon, we found that MOR+ DRG neurons densely innervate the bladder neck and myenteric plexus in the colon. Collectively, our findings identify the different types of DRG neurons that express MOR, DOR, and KOR, supporting their specific roles in the modulation of somatosensation and their targeting for the treatment of distinct painful conditions.

Disclosures: **M. Geron:** None. **A. Tassou:** None. **J. Niehaus:** None. **H. Zeng:** None. **G. Scherrer:** None.

Poster

PSTR022: Opioids

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant R01MH108924
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SBS Fellowship FGRA 21090311

Title: The Heterogeneity of Striatal MOR^{+}Neurons and Its Role in Nociception

Authors: *L. RAMIREZ SANCHEZ[1], M. WU[1], J. TOLLKUHN[1], B. LI[1,2];
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Westlake Laboratory of Life Sciences and Biomedicine, School of Life Sciences, Westlake University, Hangzhou, China

Abstract: The striosome compartment within the dorsal striatum (DS) was discovered several decades ago and is characterized by the expression of μ-opioid receptor (MOR). It has been implicated in reinforcement learning, regulation of motivation, and neuropsychiatric diseases. However, the precise contribution of striosomal neurons to these functions and conditions remains poorly understood. In this study, we focused on the role of the genetically identified striosomal population, characterized by the expression of MOR, in reward and aversion. While MOR neurons have traditionally been associated with driving positive reinforcement, there is a lack of empirical support for this claim. Furthermore, MOR neurons exhibit heterogeneous expression of Dopamine Receptor 1 (DRD1) or Dopamine Receptor 2 (DRD2), indicating a dual role in positive and negative reinforcement. To properly understand the function of this neuronal population and its role in behavior, we conducted: 1) Characterization of the molecular profile of striatal MOR neurons, 2) Calcium recording of their activity, and 3) Functional assays to test the rewarding and aversive properties. For the first part, we used a combination of *in-situ* hybridization (RNAscope) and RNA-seq to unveil the molecular landscape of striatal MOR cells. Then, we used fiber photometry in head-fixed mice to record calcium activity of DS^{MOR} neurons when rewarding, aversive, and nociceptive stimuli were presented. Strikingly, we observed an increase in activity in response to nociceptive stimuli and almost no change in response to rewarding stimuli, suggesting that DS^{MOR} neurons may play a role in nociception. To test this hypothesis, we employed a combination of optogenetics and chronic inhibition of DS^{MOR} in classic nociceptive assays. Our manipulations show that inactivation of DS^{MOR} increases Von-Frey threshold for paw withdrawal and latency to escape from thermal plate, while activation induces aversion. Taken together, our results indicate that DS^{MOR} neurons play a role in modulating aspects of nociceptive response.

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Poster

PSTR022: Opioids

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: D.01. Somatosensation – Pain and Itch

Support: Foundation of Shenzhen Science and Technology Innovation Committee JCYJ20200109141433384
Shenzhen Science and Technology Program KQTD20200820113040070

Title: Roles of EphB1 receptor in the development of opioid tolerance

Authors: *X.-J. SONG;
Southern Univ. of Sci. and Technol., Shenzhen, China

Abstract: Repeated exposure to opioids leads to opioid tolerance, which severely impairs the use of opioids and leads to opioid overdose. However, the molecular mechanisms of opioid tolerance remain elusive and approaches to improve the analgesic effect of opioid medications are limited. Here, we report that activation of EphB1 receptors plays a critical role in opioid antinociception by orchestrating μ-opioid receptor (MOR) trafficking. Conditional deletion of EphB1 in the excitatory neurons in the dorsal root ganglion (DRG) and spinal dorsal horn (DH) neurons enhanced the analgesic effect of intrathecal morphine injection in mice under physiological and neuropathic/cancer pain conditions. Conversely, morphine antinociception was diminished by morphine-induced activation of EphB1 receptors in DRG and the spinal cord or by intrathecal administration of EphB1 receptor activator EphrinB2-Fc. Electrophysiological studies showed that deletion of EphB1 receptors resulted in enhanced function of MOR in DRG and the DH neurons, suggesting a functional interaction between EphB1 and MOR. Mechanistically, we found that EphB1 formed a complex with MOR and G-protein couple kinase 2 (GRK2), a terminator for MOR signaling. EphB1 regulated GRK2-mediated phosphorylation of MOR at Ser^{375} and orchestrated MOR trafficking. Our findings strongly suggest that EphB1 receptor may serve as a driving force for the development of opioid tolerance through regulating and terminating MOR signaling, leading to the tolerance of opioid in antinociception.

Disclosures: **X. Song:** None.

Poster

PSTR022: Opioids

Location: MCP Hall A

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Title: Enkephalinergic neurons and opioid receptors in the ventrolateral orbital cortex regulate chronic pain and aversiveness

Authors: *Z. ZHOU, Y. CHANG, Y. LANXING;
Fudan Univ., Shanghai, China

Abstract: Objective Chronic pain is exerting profound impairment to public health worldwide with high prevalence and refractoriness currently, and patients suffering from long-term pain are often accompanied by mental diseases such as aversion, thus there is urgent command of developing more clinical treatments. Opioid peptides and receptors in brain are wild expressed in the several brain regions such as ventrolateral geniculate nucleus, amygdala and ventral tegmental area, and they have been reported to be closely associated to several functions such as the regulation of pain and negative emotions. In our previous study, we identified abundant expression of enkephalin and opioid receptors in ventrolateral orbital cortex. However, the roles of enkephalin and opioid receptors in the regulation of chronic pain and emotion remain unclear. **Methods** Chronic constriction injury of the sciatic nerve (CCI) was used to construct a model of neuropathic pain. We then applied virus tracing, drugs administration, electrophysiology recording, fluorescence in situ hybridization, chemogenetic manipulation and several behavioral tests to systematically investigate the role of the enkephalinergic neurons and opioid receptors in the regulation of the neuropathic pain and aversion. **Results** (1) Most of the enkephalinergic neurons in VLO are excitatory neurons. Activation of these neurons attenuates chronic pain and aversion directly. (2) Local administration of μ-opioid receptors agonists or δ-opioid receptors agonists in VLO alleviate neuropathic pain, but have no effect on aversive-like behaviors. (3) The analgesic effect produced by activation of enkephalinergic neurons in VLO is blocked by administration of μ-opioid receptor antagonists or δ-opioid receptor antagonists. **Conclusion** Enkephalinergic neurons and opioid receptors are the potential therapeutic targets for the clinical treatments of chronic pain and pain-related aversion.

Disclosures: Z. Zhou: None. **Y. Chang:** None. **Y. LanXing:** None.

Poster

PSTR022: Opioids

Location: MCP Hall A

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Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant F32DA055458 (Kimmey)
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Rita Allen Foundation Scholars Award in Pain

Title: Opioidergic state-control of midbrain nociception

Authors: *B. KIMMEY[1], L. EJOH[1], N. MCCALL[1], J. WOJICK[1], G. SALIMANDO[1], L. WOOLDRIDGE[1], C. OSWELL[1], M. MAHMOOD[1], C. RAMAKRISHNAN[2], K. DEISSEROTH[2], L. TIAN[3], G. CORDER[1];
[1]Psychiatry and Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [2]Psychiatry and Behavioral Sci., Stanford Univ., Palo Alto, CA; [3]Biochem. and Mol. Med., Max Planck Florida Inst. for Neurosci., Jupiter, FL

Abstract: The ventrolateral periaqueductal gray (vlPAG) facilitates pain and endogenous analgesia under different contexts via mu-opioid receptors (MORs) and enkephalin (Enk) signaling. However, our understanding of the endogenous opioid system and nociceptive cell-types in this region remains incomplete. Here, we used state-of-the-art mouse and viral genetic tools combined with behavior and in vivo optical recordings to further our understanding of vlPAG opioidergic neurocircuitry and elucidate endogenous opioid release dynamics under diverse pain conditions. We first genetically-captured and traced the nociceptive population in vlPAG to reveal its distribution and found that a preponderance of activated cells were located in posterior vlPAG. These posterior vlPAG nociceptive neurons were largely mu opioid receptor-expressing. We further found that these neurons projected broadly to other pain-associated nuclei throughout the brain, such as the rostroventral medulla, ventral tegmental area, and thalamus. Then, using fiber photometry calcium imaging, we found that vlPAG MOR neurons are acutely pain responsive and show decreased pain-related activity under conditions of protracted pain or expected pain relief in a model of placebo analgesia. We hypothesized that these effects on vlPAG MOR neuron activity corresponded with changes in Enk release, which we detected with the Enk biosensor deltaLight. Crucially, we found that Enk release is suppressed by acutely noxious stimuli, but increases following onset of tonic, protracted pain states and expected pain relief. In total, our data show that vlPAG MOR neurons are recruited by noxious stimulus exposure, but are dynamically regulated by endogenous opioid release that arises, at least in part, from vlPAG Enk-expressing neurons. Our continuing and future work is aimed at discerning the functional role of vlPAG Enk neurons in nociception and how vlPAG opioid circuitry interacts with other nociceptive brain areas across pain states.

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Poster

PSTR022: Opioids

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.10/D54

Topic: D.01. Somatosensation – Pain and Itch

Title: Chronic intrathecal co-administration of Neuropeptide Y and morphine in rats attenuate morphine-induced anti-nociceptive tolerance

Authors: *P. SINGH[1], S. GUPTA[2];
[1]All India Inst. of Med. Sci., New Delhi, India; [2]Anat., All India Inst. of Med. Sci., New Delhi, India

Abstract: Introduction: Opioids like morphine are the mainstay in the treatment of pain. However, development of tolerance to its antinociceptive effect limits its use clinically. The mechanisms underlying development of tolerance are not fully understood. Pain signals at the level of the spinal cord, modulates the release of different neurotransmitters and neuropeptides. Also, previous studies in our laboratory have shown that co-administration of calcium channel blockers attenuate morphine tolerance. Neuropeptide Y (NPY) is abundantly expressed in the dorsal horn of the spinal cord and has been reported to have anti-nociceptive effect. Consequently, the effect of NPY on morphine-induced tolerance was investigated in rats.
Methods: Male Sprague Dawley rats (275-325g) were implanted with intrathecal catheters (ReCath Co, USA). These were divided randomly into groups and administered the following drugs: Saline, Morphine (10µg), NPY (10µg) and NPY+ morphine. Behavioural assessment of anti-nociception was performed by hot-plate test daily for 9 days. Expression of NPY in the spinal cord was observed by immunohistochemistry and RT-PCR in morphine treated rats.
Result: Repeated intrathecal administration of morphine produced tolerance in the hot-plate test. Administration of NPY alone produced an antinociceptive effect which was less than morphine. However, combined administration of NPY and morphine led to a significantly higher antinociceptive effect with delayed onset of tolerance. Expression of NPY in the spinal cord not significantly altered.
Conclusion: Co-administration of NPY persistently enhanced antinociceptive effect with attenuation of tolerance. However, the expression of NPY was not significantly altered in tolerant rats in the current study. The mechanism of this effect is being analyzed currently

Disclosures: P. Singh: None. **S. Gupta:** None.

Poster

PSTR022: Opioids

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: D.01. Somatosensation – Pain and Itch

Support: R37 DA33397 (Traynor)
T32 TR004764 (Clements)
DOD CDMRP W81XWH-21-1-0771 (Kemp)

Title: Opioid positive allosteric modulators enhance methadone-mediated anti-allodynia in a rat-model of peripheral nerve injury.

Authors: *B. M. CLEMENTS[1], S. W. KEMP[2], J. R. TRAYNOR[3];
[1]Pharmacol., [2]Plastic Surgery, Univ. of Michigan, Ann Arbor, MI; [3]Pharmacology, Medicinal Chem., Univ. of Michigan Med. Sch., Ann Arbor, MI

Abstract: Chronic pain serves as a significant source of disability in the United States. Neuropathic pain is particularly disabling due to few adequate pharmacotherapy options. This limitation includes a reduced response to clinically used opioids, necessitating higher doses, and generating risks of diversion, abuse, and overdose. Therefore, patients unresponsive to neuropathic pain-specific treatments or in more severe pain require high-dose opioid therapy (and careful monitoring) or surgical options. As such, the use of opioid positive allosteric modulators (PAMs) has been proposed to allow opioid sparing and reduced negative side-effects. PAMs act on agonist-occupied receptors at a unique site from orthosteric agonists to increase agonist affinity and/or signaling. Opioid PAMs, such as BMS-986122, have been shown to increase opioid signaling *in vitro* and enhance opioid analgesia *in vivo* in acute pain models. Furthermore, these PAMs show no enhancement of opioid-induced constipation, reward, and respiratory depression. This class of compounds shows promise as adjuvants, but their extent of action in a neuropathic pain state has not been evaluated. Our objective is to assess changes in tactile allodynia following opioid administration with or without the opioid PAM BMS-986122 in animals with nerve injury. Spared nerve injury was performed in male and female Sprague-Dawley rats. Two weeks later, rats developed a robust and non-resolving tactile hypersensitivity. Animals then received either (R)-methadone (0.1-1 mg/kg, s.c.), BMS-986122 (10 mg/kg, s.c.), or both. (R)-methadone was chosen as a representative clinical opioid because it elicits the greatest response to allosteric modulation *in vitro*. At 2 hours post drug-delivery, von Frey thresholds were assessed using the up-down method. At doses of (R)-methadone where no reversal from baseline was seen (0.1-0.32 mg/kg, s.c.), co-administration of BMS-986122 provided an anti-allodynic effect dependent on the dose of (R)-methadone. At doses where (R)-methadone alone elicited a full reversal (1 mg/kg, s.c.), co-administration of BMS-986122 did not further increase responding. Overall, these data serve as a proof-of-concept, supporting the use of opioid PAMs in a neuropathic pain population. These conclusions further support the development of more efficacious PAMs, and the investigation in diverse pain states of neuropathic origin. Funded by R37 DA33397 (J.R. Traynor), T32 TR004764 (B.M. Clements), and DOD CDMRP W81XWH-21-1-0771 (S.W.P. Kemp).

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Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

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Program #/Poster #: PSTR023.01/D56

Topic: D.05. Auditory and Vestibular Systems

Support: JSPS KAKENHI 21K06442
JSPS KAKENHI 24K09697
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JSPS KAKENHI 19H05222
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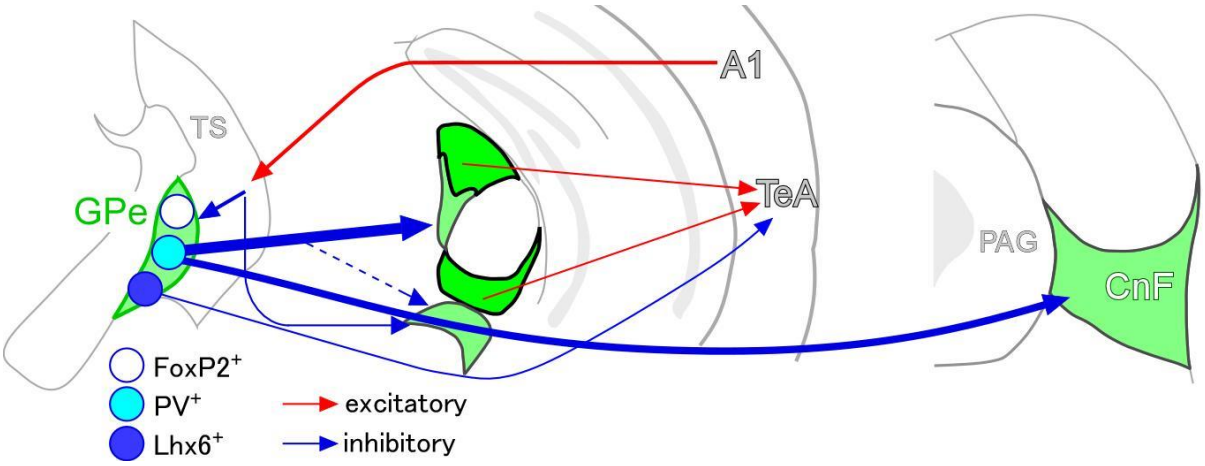
Cooperative Study Program 22NIPS129
Cooperative Study Program 23NIPS124

Title: The external globus pallidus as the hub of the auditory cortico-basal ganglia loop

Authors: *R. TOMIOKA[1], N. SHIGEMATSU[2], T. MIYASHITA[3], Y. YOSHIMURA[4], K. KOBAYASHI[5], Y. YANAGAWA[6], N. TAMAMAKI[7], T. FUKUDA[8], W.-J. SONG[9]; [1]Kumamoto Univ., Kumamoto, Japan; [2]Dept. of Anat. and Neurobio. Grad. Sch. of Life Sci., Kumamoto Univ., Kumamoto, Japan; [3]Teikyo Univ., Tokyo, Japan; [4]Natl. Inst. For Physiological Sci., Okazaki, Aichi, Japan; [5]Natl. Inst. For Physiological Sci., Okazaki, Japan; [6]Genet. and Behavioral Neurosci., Gunma Univ. Grad. Sch. of Med., Maebashi, Japan; [7]Grad Sch. Med. Sci., Kumamoto Univ., Kumamoto, Japan; [8]Dept Anat. and Neurobio., Kumamoto Univ., Kumamoto, Japan; [9]Grad Sch. of Med. Sci., Kumamoto, Kumamoto, Japan

Abstract: The cortico-basal ganglia loop has traditionally been conceptualized as consisting of three distinct information networks: motor, limbic, and associative. However, this three-loop concept is insufficient to comprehensively explain the diverse functions of the cortico-basal ganglia system, as emerging evidence suggests its involvement in sensory processing, including the auditory systems. In the present study, we demonstrate the auditory cortico-basal ganglia loop by using transgenic mice and viral-assisted labelings. The caudal part of the external globus pallidus (GPe) emerged as a major output nucleus of the auditory cortico-basal ganglia loop with the cortico-striato-pallidal projections as its input pathway and pallido-cortical and pallido-thalamo-cortical projections as its output pathway. GABAergic neurons in the caudal GPe dominantly innervated the non-lemniscal auditory pathway. They also projected to various regions, including the substantia nigra pars lateralis, cuneiform nucleus, and periaqueductal gray. Considering the functions associated with these GPe-projecting regions, auditory cortico-basal ganglia circuits may play a pivotal role in eliciting defensive behaviors against acoustic stimuli.



Disclosures: **R. Tomioka:** None. **N. Shigematsu:** None. **T. Miyashita:** None. **Y. Yoshimura:** None. **K. Kobayashi:** None. **Y. Yanagawa:** None. **N. Tamamaki:** None. **T. Fukuda:** None. **W. Song:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.02/D57

Topic: D.05. Auditory and Vestibular Systems

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Deutsche Forschungsgemeinschaft SPP Loops
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NRW Netzwerk iBehave

Title: Depolarisation state- and cell type-specific regulation of medium spiny neurons in tail of striatum by projections from auditory thalamus

Authors: L. M. HAETZEL, *J. GRUNDEMANN;
German Ctr. for Neurodegenerative Dis. (DZNE), Bonn, Germany

Abstract: The striatum integrates inputs from nearly all cortical and thalamic regions to optimise behavioural strategies. This is particularly well studied in the rostral striatum. Caudal striatal regions, such as tail of striatum (TS), have received less attention. TS exhibits unique cell-type distributions and input patterns, including projections from auditory cortex (AC) and auditory thalamus (medial geniculate body; MGB). This suggests a role for TS in auditory processing to support learning. While plasticity in AC-TS projections has been observed in an auditory discrimination task, the physiology of MGB-TS synapses is not well understood. The goal of this study was to determine how MGB afferents modulate medium spiny neuron (MSN) activity in TS. We recorded ex vivo from Drd1a-positive and Drd1a-negative MSNs in TS while

optogenetically activating MGB inputs. Each MSN was subject to two recording protocols: (1) depolarizing current steps with and without light pulse and (2) a single light pulse followed by a pulse train. MGB neurons formed direct inputs onto both Drd1a-positive and Drd1a-negative MSNs. These inputs evoked a mix of excitatory and inhibitory postsynaptic potentials (PSPs), with a prevalence of mixed PSPs in Drd1a-positive MSNs. Firing rate was affected across all MSNs, with thalamostriatal activation increasing action potential frequency specifically during high depolarisation states. Finally, we found that MGB activation modulated latency to first spike and inter-spike interval depending on MSN type and depolarisation state. Together, these results suggest that thalamostriatal synapses in TS differentially transmit information depending on postsynaptic cell type and depolarisation state. This will be pertinent for thalamostriatal processing during learning and behaviour.

Disclosures: **L.M. Haetzel:** None. **J. Grundemann:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.03/D58

Topic: D.05. Auditory and Vestibular Systems

Support: NIDCD/NIH R01DC013817
DoD RH200052

Title: Repurpose to Restore: Investigating Raloxifene's Impact on Noise-Induced Hidden Hearing Loss

Authors: *R. AMANIPOUR, B. SHUSTER, B. MILON, R. HERTZANO;
NIH, NIDCD, Bethesda, MD

Abstract: Exposure to loud noise can lead to permanent elevation of hearing thresholds. Recent studies demonstrate that exposure to noise that doesn’t permanently elevate auditory thresholds can still cause permanent damage to or loss of synaptic connections between inner hair cells and afferent nerve fibers. This deficit results in a milder form of hearing loss known as noise-induced hidden hearing loss (NIHHL, or cochlear synaptopathy). Currently there are no FDA-approved therapeutics to treat or reverse NIHHL. Our laboratory previously demonstrated the otoprotective effects of 17β-estradiol (E2) against NIHHL in ovariectomized female mice. Additional evidence suggests that the protective effects of E2 may be mediated through estrogen receptor β (ESR2). Selective estrogen receptor modulators (SERMs) are compounds that exert tissue-specific actions via ESR2. Raloxifene is an FDA-approved SERM, used to treat osteoporosis and reduce the risk of breast cancer in post-menopausal women. However, its mechanism of action in the inner ear, including its potential role as an ESR2 agonist, remains unknown. This study aims to assess raloxifene's efficacy as a therapeutic agent for NIHHL in gonadally intact female mice.B6CBAF1/J mice were obtained at 7 weeks of age. At 8 weeks of age, 21-day-slow-release

pellets containing placebo or Raloxifene were subcutaneously implanted. At 9 weeks of age, baseline auditory brainstem response (ABR) and distortion product otoacoustic emission (DPOAE) thresholds were established. At 10-weeks of age, mice were noise exposed (97 dB SPL, 8-16 kHz, 2 h). ABR and DPOAE thresholds were quantified 24 hours, 1 week, and 6 weeks post-noise exposure. At each timepoint, cochlear tissue was collected for histological analysis of cochlear synaptopathy.Treatment with Raloxifene resulted in reduced ABR threshold shifts at 1-day and 6-weeks after noise exposure. Additionally, ABR wave-I amplitude was significantly reduced at 1-week and 6-week intervals post-exposure, while treatment with Raloxifene ameliorated the reduction in ABR wave-I amplitudes. DPOAE threshold analysis found no differences between treated and placebo groups. Histological analysis at 1-day and 1-week post-noise exposure showed synaptic loss at 24 and 32 kHz in both groups, with no significant differences in the Raloxifene-treated group.These findings suggest that Raloxifene could offer partial protection against NIHHL in gonadally intact female mice. Based on these results, systemic administration of Raloxifene could be explored in pre-clinical studies focused on preserving hearing in females.

Disclosures: **R. Amanipour:** None. **B. Shuster:** None. **B. Milon:** None. **R. Hertzano:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

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Program #/Poster #: PSTR023.04/D59

Topic: D.05. Auditory and Vestibular Systems

Support: NIDCD Z01 DC000091

Title: Mechanisms Underlying Serotonergic Excitation in Medial Olivocochlear Neurons of the Descending Auditory System

Authors: *K. SUTHAKAR, C. J. WEISZ;
NIDCD, NIH / NIDCD, Bethesda, MD

Abstract: Medial olivocochlear (MOC) neurons are located in the auditory brainstem and directly inhibit outer hair cell electromotility via specialized nicotinic acetylcholine receptors, resulting in decreased cochlear sensitivity. The MOC system is functionally implicated in protection from acoustic trauma, selective attention, and signal extraction in noisy environments. MOC neurons are putatively modulated by synaptic input from various auditory and non-auditory brain regions. However, it is unclear how these heterogeneous inputs contribute to MOC neuronal activity. Given the proposed role of these neurons in context-dependent tasks, we are interested in investigating the non-auditory modulation of MOC activity via serotonin (5-HT).
We use the ChAT-IRES-Cre;tdTomato mouse model for identification of cholinergic MOC neurons. Anatomical investigations consisted of retrograde tracer injections into the cochlea

and/or immunohistochemistry for markers of 5-HT. In-vitro patch clamping from brainstem slices was combined with exogenous application of 100µM 5-HT to characterize serotonergic responses in MOC neurons. Pharmacological experiments were performed using 50µM ZD7288 to block hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which have been mechanistically implicated in 5-HT signaling in other auditory brainstem neurons.
Histological data validated the existence of serotonergic terminals in close apposition to both retrogradely-labeled and genetically-identified MOC neurons in mouse. In patch-clamp experiments, 5-HT increased MOC excitability as evidenced by increased action potential (AP) firing rate, decreased rheobase, and decreased AP threshold. Additionally, less stimulation was required to evoke a given AP firing rate in MOC neurons in the presence of 5-HT. Preliminary pharmacological experiments demonstrated that 5-HT-mediated increases in MOC excitation were retained when HCN channels were blocked by ZD7288. To further explore the underlying mechanism of action, experiments investigating the contribution of multiple voltage-gated potassium channels are ongoing.
We have shown that serotonin plays a role in modulating MOC neuron excitability in-vitro. Current experiments are focused on further probing the mechanism of action underlying the increase in MOC neuron excitability using pharmacology. These data will aid in our understanding of MOC activation and will eventually improve our understanding of how factors such as mood and attention are involved in modulating MOC responses in complex listening situations including the presence of background noise.

Disclosures: K. Suthakar: None. **C.J. Weisz:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.05/Web Only

Topic: D.05. Auditory and Vestibular Systems

Support: Fondi BRIC INAIL 2022

Title: The cross-talk between oxidative stress and inflammation in the auditory system damage: role of glial cell and macrophage activation in a model of neuro/ototoxicity

Authors: *F. PACIELLO[1], A. PISANI[2], R. MONTUORO[3], V. MOHAMED HIZAM[3], G. BONI[3], C. RIPOLI[4], A. R. FETONI[2], C. GRASSI[5];
[1]Catholic Univ. Sch. of Med., Rome, Italy; [2]Univ. of Naples Federico II, Naples, Italy; [3]Catholic Univ. Sch. of Medicine, Rome, Italy, Rome, Italy; [4]Inst. of Human Physiol., Catholic Univ. Sch. of Medicine, Rome, Italy, Roma, Italy; [5]Dept. of Neurosci., Univ. Cattolica, Rome, Italy, Rome, Italy

Abstract: The cross-talk between oxidative stress and inflammation in the auditory system damage: role of glial cell and macrophage activation in a model of neuro/ototoxicity

Fabiola Paciello[1], Anna Pisani[2], Raffaele Montuoro[3], Veronica Mohamed-Hizam[3], Giammarco Boni[1], Cristian Ripoli[1], Anna Rita Fetoni[2], Claudio Grassi[1]
[1]Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy;[2]Department of Neuroscience, Unit of Audiology, Università degli Studi di Napoli Federico II, Naples, Italy;[3]Department of Head and Neck Surgery, Università Cattolica del Sacro Cuore, Rome 00168, Italy.
Oxidative stress and inflammation are supposed to be the main mechanisms of damage in the auditory system, leading to functional deficits and hearing impairment. Glial cell, including microglia and astrocytes have been demonstrated to mediate the link between oxidative and inflammatory injury in the central nervous system. However, the role of glial cells in sensory damage, such as in the auditory system, is still elusive. In this study, we investigated the role of glial cells in mediating the toxic effect induced by styrene, a volatile compound with well-known oto/neurotoxic properties, in both the cochlea and the auditory cortex (ACx).To this aim, male adult Wistar rats were treated with styrene (400 mg/kg daily for 3 weeks, 5/days a week). At the end of treatment (day 21) we collected both the cochlea and ACx to perform electrophysiological, morphological, immunofluorescence and molecular analyses. Our results showed that the oto/neurotoxic damage induced by styrene caused a redox imbalance in both structures analyzed. This was associated with an activation of macrophage and glial cells, together with a rise of inflammatory markers (i.e., pro-inflammatory cytokines and chemokine receptors) and alterations in connexin (Cxs) and pannexin (Panx) expression. Specifically, we found a significant decreased level of Cx26 and Cx30 in the cochlea, and an upregulation of Cx43 and Panx1 in the ACx, probably responsible for an alteration of the microglia/astrocytes network. Collectively, our results provide novel insights on the role of macrophages and astrocytes in mediating the oxidative/inflammatory damage induced by styrene in both the cochlea and ACx. Our data suggest that targeting glial cells and connexin/pannexin expression might be useful to attenuate oxidative/inflammatory injury in the auditory structures, mitigating hearing loss.

Disclosures: **F. Paciello:** None. **A. Pisani:** None. **R. montuoro:** None. **V. Mohamed Hizam:** None. **G. Boni:** None. **C. Ripoli:** None. **A.R. Fetoni:** None. **C. Grassi:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.06/D60

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant R01DC008983
NIH Grant RF1MH114112
NIH Grant MH116990
NIH Grant EY019049
NIH Grant MH116990

Title: A distributed auditory network mediated by the pontine central gray underlies rapid awakening in response to alerting sounds

Authors: *J. WEI[1], C. XIAO[2], G. ZHANG[3], L. SHEN[4], H. W. TAO[5], L. I. ZHANG[1];
[1]USC, Los angeles, CA; [2]Neurosci., USC, Los angeles, CA; [3]Dept. of Neurosci. and Physiol., USC, HACIENDA HEIGHTS, CA; [4]Zilkha Neurogenetic Inst., USC, LOS ANGELES, CA; [5]Physiol. and Neurosci., USC Keck Sch. Med., Los Angeles, CA

Abstract: Animals in sleep can be waken up rapidly by external threat signals, an essential defense mechanism for survival. However, neuronal circuits underlying the fast transmission of sensory signals for this process remain unclear. Here, we report in mice that aversive sound can induce awakening within hundreds of milliseconds, for which glutamatergic neurons in the pontine central gray (PCG) play an important role. These neurons exhibit higher sensitivity to auditory stimuli in sleep than wakefulness. Suppressing these neurons results in reduced sound-induced awakening and increased sleep in intrinsic sleep/wake cycles, whereas their activation induces rapid awakening from sleep and accelerates awakening from anesthesia. Additionally, the sound-induced awakening can be attributed to the propagation of auditory signals from PCG to multiple arousal-related regions including the mediodorsal thalamus, lateral hypothalamus and ventral tegmental area. Thus, PCG serves as an essential distribution center to synergize a global auditory network to promote rapid awakening.

Disclosures: J. wei: A. Employment/Salary (full or part-time):; University of southern california. **C. xiao:** A. Employment/Salary (full or part-time):; University of southern california. **G. Zhang:** A. Employment/Salary (full or part-time):; University of southern california. **L. Shen:** A. Employment/Salary (full or part-time):; University of southern california. **H.W. Tao:** A. Employment/Salary (full or part-time):; University of southern california. **L.I. Zhang:** A. Employment/Salary (full or part-time):; University of southern california.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.07/E1

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant 1F31MH136695
NIH Grant R01 NS122840
Whitehall Foundation

Title: The role of nigrostriatal dopamine in hallucination-like percepts in mice

Authors: *J. D. ANAIR[1], J. G. PARKER[2];
[1]Northwestern Univ., CHICAGO, IL; [2]Dept. of Physiol., Northwestern Univ., Chicago, IL

Abstract: Psychotic disorders like schizophrenia and bipolar impact ~3% of people worldwide. Auditory and visual hallucinations are prominent in schizophrenia, with ~75% of patients reporting these symptoms. Canonically, excess dopamine release to the dorsomedial striatum (DMS, rodent analog of associative striatum in humans) is associated with psychosis onset. Recently, a novel behavioral assay for studying auditory hallucination-like percepts (HALIPs) in mice showed dopamine release in the tail of striatum (TS), a region that receives heavy innervation from auditory and visual centers, precedes HALIPs. Moreover, optogenetically stimulating dopaminergic fibers in the TS induces HALIPs that are blocked by antipsychotic drug treatment, suggesting an alternative striatal subregion where dysfunctional dopamine signaling may contribute to the symptoms of psychosis. To probe this circuit further, we address two major questions using an array of genetic strategies employed during the HALIP behavioral assay to address two major questions: 1) How does excess dopamine release from the principal dopaminergic input to the DMS and TS, the substantia nigra pars compacta (SNc), modulate auditory perception and its dysfunction during HALIPs? and 2) What are the relative contributions of the DMS and TS to these processes? First, to selectively drive SNc dopamine release, we used an approach established by our lab using the viral re-expression of the excitatory cation channel TRPV1 in SNc dopamine neurons of TRPV1 KO mice. Selectively activating SNc dopamine neurons in these mice via systemic injection with the TRPV1 agonist capsaicin induced dopamine release in the TS and increased the prevalence of HALIPs. Importantly, this effect was blocked by pre-treatment with the antipsychotic drug haloperidol. We are currently combining this approach with intersectional genetic strategies in the DMS and TS to delineate their respective roles in causing HALIPs. Based on the literature, we hypothesize that excess dopamine in the TS induces HALIPs, whereas excess dopamine in the DMS drives more motor-based deficits associated with schizophrenia. Taken together, our results present a novel understanding for how excess dopamine, as reported in schizophrenia, causes hallucinations and provides a gateway for developing novel therapeutic approaches for treating psychosis, based on modulation of specific dopaminergic pathways.

Disclosures: J.D. Anair: None. **J.G. Parker:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.08/E2

Topic: D.05. Auditory and Vestibular Systems

Support: IETP Toxicology Scholar program (5T32ES007326-25)

Title: Impact of combined developmental PCB and noise exposure on the cerebral microvasculature in mouse

Authors: *N. VAITHIYALINGAM CHANDRA SEKARAN[1,2], M. LOWERISON[3,2], P. SONG[3,2], S. L. SCHANTZ[4,2], D. LLANO[5,2,6];

[1]Mol. and Integrative Physiol., Univ. of Illinois, Urbana-Campaign, Urbana, IL; [2]Beckman Inst. for Advanced Sci. and Technology, Univ. of Illinois, Urbana-Champaign, Urbana, IL; [3]Electrical and Computer Engineering, Univ. of Illinois, Urbana-Champaign, Urbana, IL; [4]Dept. of Comparative Biosciences, Univ. of Illinois at Urbana-Champaign, Urbana, IL; [5]Mol. and Integrative Physiology, Univ. of Illinois at Urbana-Champaign, Urbana, IL; [6]Carle Illinois Col. of Med., Urbana, IL

Abstract: Exposure to environmental toxins such as polychlorinated biphenyls (PCBs) is widespread via multiple routes such as air, soil and water because of their stability and resistance to degradation. It was previously observed that the effects of developmental PCB exposure demonstrated that PCBs impact both central and peripheral auditory systems independently and PCB exposures can combine with later noise exposure to produce supra-additive effects on the auditory system. Previous work has also shown that developmental PCB exposure impacts endothelial cell function. Thus, the current goal is to study how combined sequential exposure to PCBs and environmental noise stress impact the microvasculature of the auditory system. The current study used super-resolution ultrasound localization microscopy (ULM) as a novel tool to measure microvascular dynamics in the auditory system. Female CBA/CAJ were dosed orally with 6 mg/kg/day of the PCB dissolved in corn oil vehicle 4 weeks before breeding and dosing was continued through gestation and until postnatal day (PND) 21. On PND 21, pups were weaned, and two males from each litter were randomly selected for the study. As adults at the age of P90, the male mice were exposed to high-intensity noise for 45 minutes at 110 dB. We examined the impact of hearing using auditory brainstem responses (ABR) after the developmental PCB exposure at pre and post-noise exposures. The hearing threshold was again tested on day 7 post noise exposure to determine if the PCB has any effect on hearing recovery after noise exposure and which is associated with blocking hearing recovery. We established our capacity to image the microvasculature of the inferior colliculus (IC) of this model, which will allow us to assess PCB and noise effects on this structure. The first IC imaging using ULM was established using a cranial window which can allow us to image longitudinally. We applied ULM imaging to a mouse model exposed to PCB and quantified differences in cerebral vascularity, blood velocity, and vessel tortuosity across the midbrain and other brain regions. Vascular structures identified with ULM were validated with histology of the same brain with FITC. The blood supply to the medial IC flows from the paramedian branch of the basilar artery. The lateral IC receives blood supply from additional pathways. This work will provide new insights into understanding the microvascular effects in the central auditory system of an environmental toxin and subsequent stressor exposed model.

Disclosures: N. Vaithiyalingam Chandra Sekaran: None. **M. Lowerison:** None. **P. Song:** None. **S.L. Schantz:** None. **D. Llano:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.09/E3

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant R01 HD111753
DoD CDMRP Tuberous Sclerosis Complex Research Program (TSCRP) Award
HT9425-23-1-0275

Title: Auditory system development in genetically distinct rat models of autism.

Authors: *M. INAMDAR[1], L. HART[2], N. JAMES[3], B. D. AUERBACH[4];
[1]Mol. and Integrative Physiol., Univ. of Illinois Urbana Champaign, Urbana, IL; [2]Mol. and Integrative Physiol., Univ. of Illinois Urbana-Champaign, Urbana, IL; [3]Molec, Univ. of Illinois Urbana Champaign, Urbana, IL; [4]Mol. & Integrative Physiol., Univ. of Illinois at Urbana-Champaign, URBANA, IL

Abstract: Despite great progress in identifying genetic variations associated with increased prevalence of autism spectrum disorders (ASD), the challenge now is to determine if these mutations converge on common mechanisms that can account for the diverse phenotypes that define ASD. One potential convergence point may be during early life critical periods, a time in early post-natal development when neural circuits are extremely plastic and drastically shaped by sensory experience. Altered critical periods may be particularly important for atypical sensory processing in ASD, a defining feature of the disorder that greatly impacts quality of life. To test this hypothesis, we characterized the development of critical period markers in rat models of Fragile X syndrome (FXS) and Tuberous Sclerosis Complex (TSC), the two most common genetically defined causes of ASD that we have previously shown to exhibit opposite cellular phenotype but may also present with similar auditory processing deficits. Specifically, we used neuroanatomical analysis to examine parvalbumin positive (PV^+) interneuron and perineuronal nets (PNN) expression in the auditory cortex (ACx) of a *Fmr1*^{KO} rat model of FXS and a *Tsc2*$^{+/-}$ Eker rat model of TSC across developmental time-points. We chose to focus on these structures because the maturation of PV^+ inhibitory interneurons and their envelopment by PNNs is thought to be a major driver of critical period closure. Preliminary results suggest that there are indeed differences in PV^+ expression, PNN expression, and PV+/PNN co-localization in the ACx of *Tsc2*$^{+/-}$ and *Fmr1*^{KO} rat models. These results indicate that shared auditory symptoms in FXS and TSC could be related to changes in the developmental time-course of PV^+ and PNN expression in the ACx.

Disclosures: **M. Inamdar:** None. **L. Hart:** None. **N. James:** None. **B.D. Auerbach:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.10/E4

Topic: D.05. Auditory and Vestibular Systems

Support: NIY Grant R01DC018353
Nancy Lurie Marks Family Foundation Collaborative Grant
Amelia Peabody Scholarship
Harvard Center on the Developing Child Science and Innovation Fellowship

Title: Vasoactive Intestinal Peptide Signaling Within Auditory Cortex

Authors: *C. LIU[1,2], C. G. SWEENEY[1], A. E. TAKESIAN[1,2];
[1]Eaton Peabody Labs., Massachusetts Eye and Ear, Boston, MA; [2]Grad. Program in Speech and Hearing Biosci. and Technol., Harvard Med. Sch., Boston, MA

Abstract: Uncovering neural targets that gate sensory cortical plasticity holds significant promise, presenting potential avenues for reshaping neural circuitry. Work from our lab and others have demonstrated that a group of cortical GABAergic neurons expressing vasoactive intestinal peptide (VIP) regulates sensory plasticity. Although many studies have leveraged the expression of VIP to genetically target this specific interneuron population, few have evaluated the function of the non-classical signaling molecule VIP in sensory processing and plasticity. We used a GPCR-Activation-Based (GRAB) peptide sensor and *in vivo* fiber photometry to study the release of VIP in mouse auditory cortex (ACtx) during passive sound presentation and across associative auditory learning. Sound stimuli elicited VIP sensor responses in ACtx from a subset of mice. Furthermore, as mice learned to associate specific sounds with reward, VIP release was modulated by the behavioral relevance of the sound stimuli. These experiments demonstrate that VIP release *in vivo* may be part of a dynamic cortical circuit that underlies sensory associative learning. In parallel, we are performing experiments to evaluate the postsynaptic effects of VIP release in ACtx. Using *in situ* hybridization, we quantified the expression levels of mRNA encoding the VIP receptor 1, *Vipr1*, across ACtx. Consistent with previous studies in other sensory cortices, we found that *Vipr1* is expressed within 77% of excitatory pyramidal cells, marked by expression of vesicular glutamate transporter 1 (*Slc17a7*) and 18% of GABAergic neurons, marked by expression of the GABA synthesizing enzymes *Gad1* and *Gad2*. Using *in vitro* calcium imaging, we demonstrated that bath application of VIP increases auditory cortical activity in response to electrical stimulation of the thalamic afferents. Ongoing whole-cell electrophysiology experiments suggest that layer 5 pyramidal neurons in ACtx show increased thalamic-evoked excitatory postsynaptic potentials following repeated VIP application. Together, these results may elucidate the effects of VIP within auditory cortical circuits, laying the necessary foundation for future loss- and gain-of-function experiments to evaluate the function of VIP release in auditory perception and learning.

Disclosures: C. Liu: None. **C.G. Sweeney:** None. **A.E. Takesian:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

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Program #/Poster #: PSTR023.11/E5

Topic: D.05. Auditory and Vestibular Systems

Support: R01DC016599
R01DC013073

Title: Modulation of auditory thalamocortical sensory transmission by the relative timing of TRN and collicular stimulation.

Authors: B. A. IBRAHIM[1], ***D. LLANO**[2];
[1]Mol. and Integrative Physiol., The Univ. of Illinois Urbana-Champaign, Urbana, IL; [2]Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Despite the critical role of the thalamus in transmitting sensory information from lower sensory structures to the higher cortical centers, how the thalamus modifies ascending information is still unclear. The diversity of the thalamic interactions with sensory and non-sensory brain areas indicates that thalamic function is modulated by multiple brain regions. For instance, the GABAergic sheet of neurons called thalamic reticular nucleus (TRN), which surrounds most of the dorsal part of the thalamus, has synaptic connections with thalamocortical and corticothalamic projections as well as with the non-sensory parts of the forebrain. Most of the studies done on the TRN focused more on the reciprocal thalamic-TRN connection through a closed-loop model, which explains the well-known oscillatory phenomena in the thalamus. However, the diverse connections between TRN and other non-sensory brain regions could indicate the presence of nonreciprocal or open loop organization, which could provide a platform for modulating the thalamocortical transmission of sensory information through modulating the relative timing between TRN stimulation and thalamic sensory stimulation. The colliculo-thalamo-cortical (CTC) slice, which preserves the synaptic connection between the inferior colliculus (IC), medial geniculate body (MGB), and auditory cortex (AC), was used to examine the change in AC activity following the change in the relative timing between the electrical stimulation of the IC and the laser photostimulation of caged glutamate at the TRN. Initially, the connection between TRN and MGB in the CTC slice was confirmed by mapping the inhibitory postsynaptic currents (IPSCs) recorded from MGB cells by laser photostimulation of the caged glutamate through a grid spanning the two structures. The presence of thalamic IPSCs produced by stimulating TRN (with shorter latency) or MGB (with longer latency) indicated the thalamic-TRN connection in the CTC slice. The AC activity was then monitored by imaging the Ca-signals from the CTC slice following the IC electrical stimulation and the laser photostimulation of caged glutamate at the TRN level. While simultaneous stimulation of the IC and TRN resulted in the suppression of the AC activity, the AC activity was enhanced when the TRN stimulation preceded the IC stimulation by 100 ms. This data indicates the possible role of TRN in modulating the thalamocortical transmission of sensory information, which could be explained by the open-loop model of TRN connections.

Disclosures: B.A. Ibrahim: None. **D. Llano:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.12/E6

Topic: D.05. Auditory and Vestibular Systems

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Hearing Health Foundation Emerging Research Grant
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Title: Unipolar brush cells shape DCN activity in vitro and in vivo

Authors: *C. CANDLER[1], T. S. BALMER[2];
[1]Arizona State Univ., Tempe, AZ; [2]Sch. of Life Sci., Arizona State Univ., Tempe, AZ

Abstract: The dorsal cochlear nucleus (DCN) receives acoustic signals from the auditory nerve, as well as non-auditory signals from various sources, to perform complex functions such as canceling self-generated sounds and localizing sounds relative to the head and body. Understanding how this cerebellum-like circuit processes information requires knowledge about how the different cell types in DCN are connected and how their synapses transform signals. Granule cells receive multimodal signals and project parallel fiber axons to fusiform cells, the principal output neurons of the DCN, as well as inhibitory cartwheel cells. Unipolar brush cells (UBCs) also receive multimodal input and project to other UBCs and granule cells. How UBCs process input to influence auditory processing in DCN is not well understood.

To investigate the connectivity and synaptic effects of UBCs in DCN, we made whole-cell patch-clamp recordings from fusiform cells, cartwheel cells, and vertical cells in acute brain slices from P15-24 transgenic mice that expressed channelrhodopsin-2 (ChR2) in a subtype of UBCs. Optogenetic stimulation of UBCs evoked EPSCs in fusiform and cartwheel cells with long latencies (10.50 ± 0.98 ms, mean ± SEM, n = 13) that were presumed to be polysynaptic, as expected. Surprisingly, EPSCs with short latencies (3.82 ± 0.30 ms, mean ± SEM, n = 20) were also observed. These latencies were similar to EPSCs recorded in granule cells (3.67 ms ± 0.26, mean ± SEM, n = 6), a known target of UBCs, which suggests that fusiform and cartwheel cells receive direct input from UBCs. Vertical cells did not receive input from UBCs. In current clamp, UBC stimulation drove granule, fusiform, and cartwheel cells to fire action potentials, suggesting that they have a significant influence on the activity of these cells. Confocal imaging of biocytin-filled cells revealed putative anatomically defined synaptic contacts between UBC axons and fusiform cells. To extend these findings, we will make single unit recordings from fusiform cells in head-fixed awake mice during acoustic stimulation and test how optogenetic manipulation of UBCs affects their auditory responses. This will test the impact of UBC activity on the spontaneous and evoked firing rates of fusiform cells and how they may affect their tuning curves in vivo for the first time.

We conclude that UBCs target fusiform and cartwheel cells directly, in addition to granule cells, and can drive them to fire. We will explore in vivo how this newfound connection affects fusiform cell activity. These findings reveal an additional excitatory pathway to fusiform and cartwheel cells that is likely to have a powerful influence on auditory processing in DCN.

Disclosures: C. Candler: None. **T.S. Balmer:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

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Program #/Poster #: PSTR023.13/E7

Topic: D.05. Auditory and Vestibular Systems

Title: The spatial and neurochemical characterization of perineuronal net-expressing neurons in the lateral cortex of the mouse inferior colliculus

Authors: *W. DAI[1,2], D. LLANO[1,2];
[1]Beckman Inst. for Advanced Sci. and Technol., Urbana, IL; [2]Mol. & Integrative Physiol., Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Perineuronal nets (PNNs) have been shown to serve critical roles in neuroplasticity and neuroprotection. Despite their wide distribution across the mammalian central nervous system, PNNs are not well characterized within non-lemniscal portions of the inferior colliculus (IC). The IC is the primary integration hub of the central auditory pathway, receiving and sending multimodal information across various brain regions. The lateral cortex of the IC (LC) shows a unique level of organization in the form of modules, periodic clusters of neurons with distinct neurochemical and connectional properties. In particular, the modules stain strongly for parvalbumin, cytochrome oxidase, and other markers of metabolic activity, suggesting that they may be more susceptible to oxidative stress compared to the surrounding area, or matrix. The present study seeks to determine if PNNs are found more commonly in modules compared to matrix as a potential defense mechanism against increased oxidative stress, and if PNNs are upregulated as an animal ages due the accumulation of oxidative species. To answer these questions, transgenic mice expressing GFP in GAD67-expressing neurons were processed, and LC-containing sections were stained for parvalbumin and PNNs. Neuronal soma were quantified based on the combination of markers they stained positively for and their location in the module-matrix organization. Statistical analyses were conducted to identify any significant differences in the proportion of cell-types between modules and matrix, as well as any significant trends with age. We found that for all GABAergic cell-types, the modules comprise a greater percentage of neurons that stained for other markers, including PNNs, compared to the matrix. The only exception was neurons that expressed GABA only, with the matrix comprising a greater percentage of these neurons. Additionally, we found that as a mouse ages, the only cell-type that appears to show a significant trend is GABAergic, PNN-expressing neurons in the modules, which increase in percentage with age. Together, these data suggest that the modules of the LC are upregulated in PNNs due to the increased metabolic activity and risk of oxidative stress present, further elucidating the functional differences between modules and matrix and the role of PNNs in the auditory pathway and their potential involvement in diseases with disturbances in oxidative stress.

Disclosures: W. Dai: None. **D. Llano:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

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Program #/Poster #: PSTR023.14/E8

Topic: D.05. Auditory and Vestibular Systems

Title: The Foxp2 Influence on the Developing Auditory Pathway

Authors: *M. JANKOVIC[1], A. J. HOLLEY[2], J. R. GIBSON[3], G. KONOPKA[2];
[2]Neurosci., [1]UT Southwestern Med. Ctr., Dallas, TX; [3]Dept. of Neurosci., UT Southwestern, Dallas, TX

Abstract: Sensory processing abnormalities, are critical features of neurodevelopmental disorders (NDDs), including autism spectrum disorder, affecting quality of life and maladaptive sensory behaviors. The transcription factor Foxp2, linked to NDDs and speech disorders, has a notable expression pattern in auditory processing regions of the brain. Foxp2 has selective expression in the brain including several areas involved in the auditory processing pathway including corticothalamic projection neurons and cells in the inferior colliculi (IC), a midbrain region crucial in auditory processing. Preliminary studies of the loss of Foxp2 in the mouse show alterations in cortical auditory responses and loss of dopamine receptor expressing neurons in the cortex. Our data indicate significant changes in the proportion of specific neuronal populations and sensory gating deficits in the IC of Foxp2-deficient mice, underscoring the pivotal role of Foxp2 in auditory processing. Ongoing research aims to understand the cellular and circuit changes caused by the loss of Foxp2 in the cortex and IC separately. Investigating two regions and multiple key timepoints, we are carrying out single nuclei transcriptomic and chromatin accessibility experiments to identify unique and overlapping genes and regulatory regions downstream of Foxp2 in the development of each region. We are also using ex vivo electrophysiological recordings to identify changes in cell and circuit function of single and paired cells to determine synapse dysregulation and/or cellular excitability alterations caused by the loss of Foxp2. By detailing the transcriptomic and electrophysiological landscape shaped by Foxp2, our data advance our understanding of sensory processing deficits in NDDs.

Disclosures: M. Jankovic: None. **A.J. Holley:** None. **J.R. Gibson:** None. **G. Konopka:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

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Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant R01 DC 019348
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Title: Convergence of bilateral auditory tectothalamic pathways

Authors: *J. KARA[1], T. T. ADEYELU[2], C. C. LEE[3];
[1]Louisiana state Univ., Baton Rouge, LA; [2]Comparative Biomed. Sci., Louisiana State Univ., Baton Rouge, LA; [3]Comparative Biomed. Sci., LSU Sch. of Vet. Med., Baton Rouge, LA

Abstract: The medial geniculate body (MGB) receives diverse and robust ascending and descending projections, making it a critical hub in the central auditory system. Ascending excitatory and inhibitory inputs to the MGB originate from the auditory midbrain (inferior colliculus: IC),which convey and regulate auditory signals. While the ipsilateral auditory tectothalamic pathways are well characterized, the contralateral tectothalamic pathways are largely unexplored. Therefore, to explore the cell-type specific organization of the contralateral pathways, we employed a cre-lox mediated, dual-anterograde, viral tracing approach using C57BL/6J, VGlut2-Cre and VGAT-Cre mice. We assessed the pattern of convergence from bilateral tectothalamic sources to characterize their topographic and convergent organization across meso- and micro-anatomical scales. Our data demonstrate a topological alignment of terminal arbors originating from bilateral tectothalamic inputs onto MGB neurons. The relative neuroanatomical weight of excitatory and inhibitory terminals from the contralateral IC suggests a substantial role in influencing MGB responses. These data are supported by ongoing optogenetic electrophysiological experiments to delineate the functional impact of these contralateral projections on the MGB and auditory processing. Overall, our data highlight overlooked roles of the contralateral tectothalamic projections in central auditory processing.

Disclosures: J. Kara: None. **T.T. Adeyelu:** None. **C.C. Lee:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

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Canada Foundation for Innovation 38337

Title: Myeloarchitectonic maps of cat auditory cortex

Authors: *A. ROBERTSON[1], B. BUTLER[2];
[1]Western Univ., London, ON, Canada; [2]Psychology, Univ. of Western Ontario, London, ON, Canada

Abstract: Delineating cortical areas and creating detailed maps of functional networks has been a central goal of neuroscientists for over a century. These efforts have contributed to our understanding of whole-brain networks that underlie behaviours and to our ability to identify patterns of atypical brain activity. Non-invasive parcellation of cortex generally relies on our understanding of typical cortical functions (e.g., via functional localizer scans), while structural parcellation often depends on highly invasive approaches (e.g., quantifying biomarkers is histological sections). However, novel neuroimaging sequences aim to provide non-invasive estimates of anatomical features, including myelin density. Here, we generate and compare a stereological myeloarchitectonic map of the feline auditory cortex to maps generated within the same animals using myelin-sensitive neuroimaging sequences (parameters obtained: OGSE, MTsat, uFA) in a 9.4T Bruker Neo scanner. Our histological results suggest unique patterns of myelination exist across the 13 feline auditory cortical areas. Moreover, myelination gradients are in accordance with a functional hierarchy previously established using patterns of interregional connectivity; core areas (primary auditory cortex and the anterior auditory field) showing the greatest myelin density, with decreasing myelination in higher-order multimodal areas. We found histological myelin content correlated significantly with non-invasive estimates of myelin across the 13 regions of interest (e.g., histology:MTsat ρ; = 0.78). These findings support previous reports concerning the hierarchical distribution of myelin across the cortex. Furthermore, they serve as evidence that regions of the auditory cortex can be delineated using these differences to create histological maps. Finally, we validate non-invasive neuroimaging sequences that purport to be sensitive to myelin, and demonstrate their utility in creating anatomical maps of cortex that may be useful in the localization of aberrant function in vivo, in neurosurgical planning, and in the study of neuroplasticity.

Disclosures: A. Robertson: None. **B. Butler:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

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Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant F32MH120890

Title: The representation of somato-motor signals in the inferior colliculus

Authors: *A. LESICKO[1], E. MICHEL[1], A. SOOTS[1], K. ADEAGA[1], M. N. GEFFEN[2]; [1]Univ. of Pennsylvania, Philadelphia, PA; [2]Otorhinolaryngology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Real-world auditory behaviors, such as vocalization, sound-driven defense behavior, and orienting movements, often extend beyond passive listening and involve complex audio-motor and multisensory integration. Within the central auditory system, the inferior colliculus

(IC) serves as an obligatory relay station and massive convergence center for auditory information. In addition to its role in sound processing, the IC receives input from diverse multisensory and neuromodulatory structures and is implicated in a variety of such acoustico-motor behaviors. However, little is known about the representation of somato-motor signals within the IC and their functional role in auditory behavior. In this study, we performed two-photon imaging in the IC while recording the spontaneous movements of head-fixed mice and presenting a variety of sound stimuli. Video recordings were analyzed using FaceMap and DeepLabCut and neurons that were responsive to either sound, movement, or both were parsed using a generalized linear model. We found that movement was robustly encoded in the IC, with movement-responsive neurons surprisingly outnumbering sound-responsive neurons. Most movement-responsive neurons responded to facial or ear movements, with fewer responding to movements of the limbs or trunk, and many neurons encoded movement from multiple body regions. To further investigate how somato-motor inputs affect auditory behavior, we trained mice to perform a go/no-go sound detection task in which they lick for a water reward during the presentation of a noise target stimulus. Once mice reached a performance criterion of 80% correct on behavioral training, the amplitude of the noise target was systematically varied to determine their detection thresholds and they were moved into a testing phase in which somato-motor inputs to the IC were optogenetically activated on a subset of trials. Preliminary data showed that activation of somato-motor inputs to the IC led to a decrease in performance accuracy on the sound detection task. Finally, we performed anterograde trans-synaptic labeling of neurons in the IC that receive somato-motor input. We found axon fibers from trans-synaptically labeled IC neurons in the medial geniculate body, laterodorsal tegmental nucleus, contralateral lateral cortex of the IC, and the superior colliculus, suggesting that IC neurons that receive somato-motor input project to regions involved in auditory and motor processing. Together, these experiments demonstrate robust somato-motor encoding and modulation of auditory information in the IC.

Disclosures: **A. Lesicko:** None. **E. Michel:** None. **A. Soots:** None. **K. Adeaga:** None. **M.N. Geffen:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

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Topic: D.05. Auditory and Vestibular Systems

Support: NIH F32DC018211
NIH R01DC018353

Title: Reliable sensory processing of superficial cortical interneurons is modulated by behavioral state and local networks

Authors: *C. SWEENEY[1], M. THOMAS[2], L. G. VATTINO[3], A. E. TAKESIAN[4];
[1]Mass Eye and Ear/Harvard Med. Sch., Boston, MA; [2]Mass Eye and Ear, Boston, MA; [3]Otolaryngology Dept., Mass Eye and Ear - Harvard Med. Sch., Boston, MA; [4]Otolaryngology, Massachusetts Eye and Ear, Boston, MA

Abstract: The GABAergic inhibitory interneurons that populate the outermost layer of superficial sensory cortex are sites of convergence for bottom-up sensory and top-down contextual signals that powerfully regulate cortical network activity and plasticity. However, little is known about how these interneurons process sensory information. We performed two-photon calcium imaging in awake mice to record the responses of two superficial cortical interneuron populations in superficial auditory cortex, VIP and NDNF interneurons, to simple and complex sound stimuli and compared these responses to those recorded in layer 2/3 pyramidal neurons. We find that VIP and NDNF interneurons respond robustly to sound, however with less trial-to-trial reliability than pyramidal neurons. Interestingly, VIP and NDNF interneurons display sharp tuning for the stimuli to which they show reliable responses. VIP and NDNF interneurons exhibit stronger within-population noise correlations than pyramidal neurons, suggesting that robust non-auditory inputs to these neurons or strong interactions within these interneuron networks may underlie the low reduced reliability. Indeed, the magnitude and reliability of sound-evoked responses of these interneurons are increased during locomotion, suggesting that their activity is modulated by top-down inputs that convey behavioral state. This study demonstrates the diversity of the in vivo responses of VIP and NDNF interneurons, and points to the state-dependent modulation of reliability as a potential mechanism by which superficial cortex relays contextual cues.

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Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

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Topic: D.05. Auditory and Vestibular Systems

Support: US Department of Veteran Affairs 1I01 RX001095
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Title: Dynamic changes in post-synaptic markers of central neurotransmission in a model of noise-induced temporary threshold shift

Authors: *S. YALCINOGLU[1], R. D. BRAUN[1], T. KARAM[2], A. HOLT[1,3];
[1]Wayne State Univ. Sch. of Med., Detroit, MI; [2]Wayne State Univ., Detroit, MI; [3]John D Dingell VAMC, Detroit, MI

Abstract: Our previous imaging studies using the calcium surrogate manganese (Mn^{2+}) as a marker of neuronal activity show changes in Mn^{2+} uptake after a single noise exposure (NE). This indicates a relationship between noise-induced permanent or temporary threshold shift (PTS or TTS) and increased neuronal activity in the inferior colliculus (IC). Noise-induced changes in neuronal activity may result from either pre- or post-synaptic plasticity. We have shown that L-type calcium channel (CaV) blockade prior to noise-induced TTS differentially affects peripheral and central synaptic function. These results suggest a role for dysregulation of CaVs in noise-induced hearing dysfunction. Comparing changes in post-synaptic CaVs in central auditory nuclei may provide important evidence for identifying mechanisms contributing to increased spontaneous activity that occurs after NE. Thus, in the current study we examined the distribution of CaV1.3 in auditory nuclei following noise-induced TTS and CaV blockade using verapamil. Sprague-Dawley rats were split into three groups: intraperitoneal (IP) saline injection only, IP saline injection before noise exposure, and IP verapamil injection before noise exposure. Post treatment, the noise groups were exposed to a 16 kHz, 106 dB SPL tone for one hour, while the saline group was maintained in ambient noise conditions for one hour. Five days post treatment, following transcardial perfusion, rat brains were collected, post-fixed, and cryoprotected. Serial cryostat sections (40 µm) were collected for immunolabeling. The density and intensity of immunolabeled CaV1.3 was compared in IC subdivisions across groups. In the saline only group, localization of CaV1.3 in the IC was most abundant in the external cortex and the dorsolateral portion of the central nucleus of the IC (CIC), compared to the dorsal cortex of the IC. When comparing the different groups, in the CIC no differences were found in the low frequency dorsal regions. However, in the ventral CIC, significantly more CaV1.3 labeling was observed in the noise saline group compared to both the saline only and verapamil groups ($p<0.05$). Noise exposure revealed a frequency dependent increase in CaV1.3 distribution in the CIC. The results suggest a mechanism for the increased neuronal activity observed after NE in previous studies of the IC and suggest that CaV blockade alone does not prevent noise-induced central changes in synaptic transmission. Future studies should further delineate changes in distribution and levels of CaV1.3 at different time points and across auditory nuclei following NE as well as explore different isoforms of CaVs (i.e., CaV1.2).

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Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

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Program #/Poster #: PSTR023.20/E14

Topic: D.05. Auditory and Vestibular Systems

Title: Mechanisms of Hearing Loss in a Newly Generated Mouse Model

Authors: *K. A. GRAVES[1], D. A. LLANO[2];
[1]Univ. of Illinois Urbana Champaign, Champaign, IL; [2]Molec & Integrative Physiol, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: GABAergic neurons in the inferior colliculus (IC) play a crucial role in auditory processing by extracting specific features of sounds (Ono et al., 2005). We have used a Gad67-GFP mouse model to better study the function of these neurons by using a green fluorescent protein that is expressed endogenously via the GAD67 promoter. Unfortunately, this strain of mouse is bred on a mouse strain that is known to lose hearing at a very young age. The aim of this study is to better develop a mouse model that allows for the functional examination of GABAergic neurons while retaining largely normal hearing throughout the lifespan, resembling that of the gold standard mouse model most used in hearing research. This study additionally aims to understand the mechanisms that underlie hearing loss in this animal model so that this hearing loss can be corrected. Therefore, this study will focus specifically on the hair cells (HCs) and ribbon synapses of the cochlea, which could be responsible for hearing loss in the mouse model, as well as clinical disorders, such as presbycusis. Hearing loss is easily assessed in humans via audiometric evaluation with auditory brainstem response testing (ABR) as a supplementary hearing threshold or neurodiagnostic test. Unfortunately, cochlear morphology in humans is not as easily assessed as it is in mice that have been genetically manipulated to have a hearing loss. Additionally, pure tone audiometric evaluation and speech testing is impossible to conduct in mice to draw direct comparisons of hearing thresholds in humans, which is why ABR testing is necessary. In lieu of human subjects, four different mouse models were used due to known similarities between the mouse and human genome in addition to parallels between structural components of the cochlea. Through investigation of these questions, this study has successfully developed a mouse model that allows the study of GABAergic neuron function in the IC while maintaining good hearing to better understand their contribution to auditory processing, and to also make a connection to potential other underlying causes of presbycusis in humans. Subsequent ABR testing at 6- and 12-month timepoints confirmed maintained good hearing in this new mouse model. Morphological analysis of the cochlea in each of the four strains further supported ABR threshold findings, in addition to brain histology which confirmed continued maintained expression of GFP under control of the endogenous GAD67 promoter.

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Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

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Topic: D.05. Auditory and Vestibular Systems

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Title: Functional connectivity across the human subcortical auditory system using an autoregressive matrix Gaussian copula graphical model approach with partial correlations

Authors: *K. SITEK[1], N. CHANDRA[2], B. CHANDRASEKARAN[3], A. SARKAR[4];
[1]Communication Sci. and Disorders, Northwestern Univ., Evanston, IL; [2]UT-Dallas, Richardson, TX; [3]Northwestern Univ., Evanston, IL; [4]UT-Austin, Austin, TX

Abstract: The auditory system comprises multiple subcortical brain structures that process and refine incoming acoustic signals along the primary auditory pathway. Due to technical limitations of imaging small structures deep inside the brain, most of our knowledge of the subcortical auditory system is based on research in animal models using invasive methodologies. Advances in ultra-high field functional magnetic resonance imaging (fMRI) acquisition have enabled novel non-invasive investigations of the human auditory subcortex, including fundamental features of auditory representation. However, functional connectivity across subcortical networks is still underexplored in humans, with ongoing development of related methods.

Traditionally, functional connectivity is estimated from fMRI data with full correlation matrices. However, partial correlations reveal the relationship between two regions after removing the effects of all other regions, reflecting more direct connectivity. Partial correlation analysis is particularly promising in the ascending auditory system, where sensory information is passed in an obligatory manner, from nucleus to nucleus up the primary auditory pathway, providing redundant but also increasingly abstract representations of auditory stimuli. While most existing methods for learning conditional dependency structures based on partial correlations assume independently and identically Gaussian distributed data, fMRI data exhibit significant deviations from Gaussianity as well as high temporal autocorrelation.

Here, we developed an autoregressive matrix-Gaussian copula graphical model to estimate the partial correlations and infer the functional connectivity patterns within the auditory system while appropriately accounting for autocorrelations between successive fMRI scans. Our results show strong positive partial correlations between successive structures in the primary auditory pathway on each side (left and right), including between auditory midbrain and thalamus, and between primary and associative auditory cortex. These results are highly stable when splitting the data in halves and computing partial correlations separately for each half of the data, as well as across cross-validation folds. In contrast, full correlation-based analysis identified a rich network of interconnectivity that was not specific to adjacent nodes along the pathway.

Overall, our results demonstrate that unique functional connectivity patterns along the auditory pathway are recoverable using novel connectivity approaches and that our connectivity methods are reliable across multiple acquisitions.

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Poster

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Topic: D.05. Auditory and Vestibular Systems

Support: #P20GM103408

Title: Ascorbic Acid Chiral Synthon-based Discovery of Positive Allosteric Modulators of alpha9/alpha10 nicotinic acetylcholine receptors

Authors: *J. OMAN[1], M. K. SCHULTE[2], P. SAPKOTA[2], S. YEASMIN[3], S. AKABERI[4], S. MATEEN[5], S. PASHIKANTI[5];
[1]Idaho State Univ., Pocatello, ID; [2]Biomed. and Pharmaceut. Sci., Idaho State Univ., Pocatello, ID; [3]Dept. of Biomed. and Pharmaceut. Sci., Pharm. Lab. 745C, Idaho State Univ., Pocatello, ID; [4]Idaho State Univ., boise, ID; [5]ISU, Pocatello, ID

Abstract: Hearing is a precise and complex system that utilizes efferent feedback pathways to adjust auditory function of the inner ear. These important auditory circuits are crucial for gain control of hearing. Loss of function in this system can affect hearing, greatly impacting quality of life for patients. Alpha9/alpha10 nicotinic acetylcholine receptors, found in the synapses of hair cells, play a key role in the function of these pathways. Positive allosteric modulators (PAMs), specifically ascorbic acid (AA) and ryanodine, have been previously shown to increase the amplitude of nicotinic responses to acetylcholine. Gain of function mutations of nicotinic receptors in the MOCS have been demonstrated to provide hearing protection in high noise environments. We hypothesize that selective PAMs for thealpha9/alpha10 nAChR will provide similar protection and lead to the firstpharmaceuticals for otoprotection. We performed a Structure-Activity Relationship (SAR) study to evaluate synthetic analogs of AA on subtypes of the nAChRs. Biological activity was determined using two electrode voltage clamp on Xenopus Laevis oocytes expressing alpha7, alpha4/beta2, alpha9, and alpha9/alpha10 nAChRs. We also performed studies to determine antioxidant capacity and stability of AA analogs. AA is a chiral synthon amenable for application of chiral pool strategies in design and synthesis of analogs. Alkylation of AA on the C2 and C3 - hydroxy was achievable, as well as cyclic ketal derivatives at the C5, C6 - hydroxy for synthesis of a library of compounds. Gram scale synthesis of AA derivatives was achievable and used in SAR studies. Perturbation of the enolic hydroxy acidity was modified by C5 and C6 substitution. Protection of AA's 1,2-diol did not impact the efficacy of the receptor. Reduction of AA olefin resulted in no positive allosteric modulation.

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Poster

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Title: Recurrent inhibitory networks in layer 1 of the mouse primary auditory cortex

Authors: *L. G. VATTINO[1,2], M. THOMAS[1,2], C. MACGREGOR[1], C. LIU[1,2], C. G. SWEENEY[1,2], A. E. TAKESIAN[1,2];
[1]Mass Eye and Ear, Boston, MA; [2]Harvard Medical School, Boston, MA

Abstract: Inhibitory interneurons in neocortical layer 1 (L1-INs) regulate cortical plasticity and learning, but the long-range and local cortical inputs that control the activity of these INs have not been characterized. L1-INs can be subdivided into two major classes by the expression of either neuron-derived neurotrophic factor (NDNF) or vasoactive intestinal peptide (VIP). These INs are thought to integrate sensory and neuromodulatory signals from the diverse long-range axons that populate L1. L1-INs also make inhibitory synaptic contacts with their neighbors and are connected electrically through gap junctions, suggesting that they may form complex networks. Here, we combined anatomical tracing, *in vitro* electrophysiology, and *in vivo* two-photon imaging experiments in the mouse auditory cortex to understand how specific sensory inputs recruit the L1-INs. We used monosynaptic retrograde tracing and whole-cell electrophysiology to characterize the thalamic inputs onto VIP and NDNF L1-INs within the auditory cortex. We find that the vast majority of auditory thalamic inputs to these L1-INs unexpectedly arise from the ventral subdivision of the medial geniculate body (MGBv), the tonotopically-organized primary auditory thalamus. These L1-INs receive robust functional monosynaptic MGBv inputs that are comparable in strength and short-term plasticity to those in the L4 excitatory pyramidal neurons. Activation of these thalamic axons drives robust feed-forward inhibition onto both L1-IN subtypes, but differences in feed-forward inhibition between these subtypes suggests that they receive distinct sources of inhibitory inputs. To interrogate the synaptic connectivity between the L1-IN subtypes, we performed fluorescence-guided whole-cell electrophysiology while optogenetically activating VIP or NDNF L1-INs. We found that $GABA_A$-mediated synaptic connections between NDNF neurons were significantly stronger than those between VIP neurons or other L1-INs, suggesting a robust recurrent inhibitory network within the NDNF IN subpopulation. To understand how the connectivity between neighboring NDNF L1-INs impacts *in vivo* sound processing, we activated ensembles of NDNF L1-INs in awake mice while recording the activity of the NDNF L1-IN network using two-photon calcium imaging. Strikingly, activation of small NDNF L1-INs ensembles (<7 INs) can significantly modulate the sound-evoked responses of the NDNF L1-IN population. Together, our findings show that L1-INs are embedded within complex local networks with distinct synaptic connectivity patterns that may powerfully shape the activation of these INs by sensory signals.

Disclosures: L.G. Vattino: None. **M. Thomas:** None. **C. MacGregor:** None. **C. Liu:** None. **C.G. Sweeney:** None. **A.E. Takesian:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.24/E18

Topic: D.05. Auditory and Vestibular Systems

Title: Auditory cocaine conditioning induces neuroplasticity in the early auditory system and implicates the locus coeruleus in sound-cued control of behavior

Authors: *J. ROBINSON[1,2], M. A. PRESKER, Jr.[3], M. YIP[4], S. RAJAN[4], K. M. BIESZCZAD[5];
[1]Psychology, Rutgers Univ., Old Bridge, NJ; [2]Psychology, Behavioral and Systems Neuroscience, Rutgers University, Piscataway, NJ; [3]Brain Hlth. Inst., Rutgers - The State Univ. of New Jersey, Piscataway, NJ; [4]Rutgers Univ., Piscataway, NJ; [5]Psychology, Behavioral and Systems Neurosci.; Dept. of Otolaryngology-Head & Neck Surgery, Rutgers Univ., Rutgers RWJ Med. Sch., Piscataway, NJ

Abstract: Enhanced behavioral reactivity to drug-associated cues is a primary feature of addiction that contributes to relapse vulnerability, a primary therapeutic target in addiction treatment. Substantial evidence supports a central role for mesolimbic system plasticity in addiction but little is known about the involvement of sensory systems. Here we report neuroplasticity events in sensory neural representations of drug-associated cues, offering a fresh perspective to explain the heightened behavioral response to drug-associated sensory stimuli. In recent years, the centrality of sensory systems in learning and memory has emerged, e.g., experience-dependent plasticity in the auditory system occurs over a lifetime of salient experiences with sound. Early auditory processing is intertwined with brainstem neuromodulatory structures like the locus coeruleus (LC), a prime candidate circuit mechanism for adaptive processes such as focused attention, or for maladaptive disease states, like addiction. Altered neural processing of sensory stimuli linked to drug-tasking may be fundamental to relapse risk. Here, we use the auditory brainstem response (ABR) in rats to investigate if basic sensory processing can be affected by experience with sound cues paired with cocaine administration. We report a novel behavioral assay that reveals neutral sound cues can be selectively conditioned with cocaine (auditory cocaine conditioning (AuCC): 6 daily 30-min. conditioning sessions of tone (e.g., 5 kHz, 70 dB SPL) exposure with cocaine (20 mg/kg; i.p. injection) to later control free exploratory or operant behavior. We also report sound-specific changes to auditory neural processing (using minimally invasive surface neurophysiology before vs. after AuCC) in early tone-evoked ABR timing and magnitude for sounds associated with cocaine (vs. tones associated with saline i.p. injection) that persist for at least weeks. Further, auditory-cued behavior and neural responses correlate with LC activity (measured using fos activity upon cocaine-cue exposure vs. saline cue exposure). Importantly, all behavioral and neural assessments report activity without cocaine on board, so are interpreted to be driven by the cocaine-conditioned properties of the paired tone cue. Indeed, auditory cocaine conditioning leads to sound-specific neuroplasticity in the auditory system that may maladaptively drive attention and behavior towards drug-associated cues. Overall, the findings are consistent with an emerging hypothesis that drug-induced neural plasticity in sensory systems may underpin the altered reactivity to drug-cues in cocaine addiction and in cue-induced relapse.

Disclosures: **J. Robinson:** None. **M.A. Presker:** None. **M. Yip:** None. **S. Rajan:** None. **K.M. Bieszczad:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.25/E19

Topic: D.05. Auditory and Vestibular Systems

Support: DC009836
Vatat scholarship

Title: Cochlear sensorineural damage disrupts amygdalar sound processing and auditory threat evaluation, offers insights into the affective dimensions of hearing loss and auditory hypersensitivity

Authors: *B. AWWAD[1], D. B. POLLEY[2];
[1]Harvard Med. Sch., Boston, MA; [2]Otolaryngology, Harvard Med. Sch., Boston, MA

Abstract: Acoustic trauma, characterized by sudden noise-induced injury to cochlear hair cells or primary afferent neurons, triggers a complex series of structural, transcriptional, and physiological responses in the central auditory system of adult rodents. While these compensatory mechanisms aim to restore sensitivity, they frequently lead to neural hyperactivity, potentially leading to auditory disorders such as tinnitus, hyperacusis, and impaired hearing in noisy settings. Sensorineural hearing loss (SNHL) caused by acoustic trauma is typically studied as a sensory disorder, though patient complaints emphasize significant aversion, discomfort, and anxiety triggered by moderate-intensity innocuous sounds, often leading to social withdrawal and depression. The affective dimensions of hearing loss have not been modeled in laboratory animals, so very little is known about the underlying neural substrates and mechanisms. Here, we tested the hypothesis that hyperactive efferent projections from the auditory forebrain induce hyper-responsive, non-habituating sound processing in a key sensory gateway to the limbic system, the lateral amygdala (LA). Here, we expressed GCaMP in excitatory LA neurons and monitored bulk calcium activity over a several week period with implanted fibers in awake, head-fixed mice. We found that sound evoked activity in LA habituated over several days in sham-exposed mice but became hyper-responsive and non-habituating in mice with noise-induced high-frequency SNHL. Mice then underwent a Pavlovian discriminative auditory threat conditioning protocol, which produced discriminative fear recall and selective LA plasticity in sham-exposed mice but generalized, non-extinguishing threat learning and LA plasticity in SNHL mice. Our ongoing experiments are directly testing the contribution of auditory cortex (ACtx) hyperactivity in LA plasticity, with a particular focus on whether direct activation of parvalbumin-expressing interneurons in ACtx can sustainably reinstate normal LA sound processing and auditory threat evaluation.

Disclosures: **B. Awwad:** None. **D.B. Polley:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.26/E20

Topic: D.05. Auditory and Vestibular Systems

Title: Optogenetic Deactivation of Amygdalo-Auditory Cortex Circuit

Authors: *D. C. PETERSON[1], D. A. COPAS[2];
[1]Biomed. Sci., Philadelphia Col. of Osteo. Med., Suwanee, GA; [2]Anatomy, Neurosci. & Hlth. Sci., Univ. of Findlay, Findlay, OH

Abstract: Introduction: While the functions of many amygdalar circuits have been widely studied, *the role of the direct amygdalo-auditory cortex (AM-AC) circuit is unknown.* **Objective**: Understand the function of the direct projection from the amygdala to auditory cortex. **Methods**: Two experiments were performed. In Experiment 1: Electrophysiology was utilized to record single and multi-unit responses from auditory cortex. Optogenetic activation or deactivation of the amygdalo-auditory cortex circuit was then utilized to examine changes to auditory neuron firing rate during normal and deactivation scenarios. In Experiment 2, the protocols for experiment 1 were tested in animals with a sound-induced tinnitus to determine whether deactivation of the amygdalo-auditory cortex circuit would influence the tinnitus perception. In both experiments, fluorescent labeling from the optogenetic injection was examined in the amygdala and auditory cortex. **Results**: The optogenetic vector construct provided both anterograde and retrograde labeling. The injection site was isolated to the lateral and basal nuclei of the amygdala. Labeled neurons included pyramidal and multipolar cells. Within auditory cortex, a few pyramidal neurons were observed bilaterally throughout both primary and secondary areas of auditory cortex. In addition, a large number of en-passant and terminal boutons were observed throughout layers 1-6 but prerdominantly in layers 5 and 6. Recording of neurons in auditory cortex were characterized by best frequency. Deactivation of the amygdala projection to auditory cortex caused a significant inhibition of cortical firing rates in both multiunit and single-unit recordings. This inhibition occurred only during the time of the amygdala projection deactivation. In our tinnitus animals, the tinnitus was eliminated during the amygdala projection deactivation. However, the tinnitus immediately recovered when the pathway was released from deactivation. **Conclusions**: While most of the amygdalar projection neurons to auditory cortex are pyramidal (i.e., glutamatergic), the overall influence of the pathway was inhibitory. Therefore, this pathway is likely to contact inhibitory circuits within cortex. The timing of inhibition and release from inhibition occurred within a manner of milliseconds. No long-term effects were observed. Therefore, we hypothesize that the amygdalo-auditory cortex circuit may provide quick modulatory influences on cortex that may help to prime cortical circuits for subsequent inputs from the nucleus basalis (a projection that has longer-lasting influences on cortical function).

Disclosures: **D.C. Peterson:** None. **D.A. Copas:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.27/E21

Topic: D.08. Multisensory Integration

Support: NIH Grant F32MK127788
Kaufman Foundation Grant KA2020-114796
NIH Grant R01DC015527
NIH Grant R01DC014479
NIH Grant R01NS113241

Title: Direct piriform-to-auditory cortex projection contributes to auditory-olfactory integration

Authors: *N. W. VOGLER[1], R. CHEN[2], A. VIRKLER[2], J. A. GOTTFRIED[3], M. N. GEFFEN[1];
[1]Otorhinolaryngology, [3]Dept. of Neurol., [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: In complex environments, the brain must integrate information from multiple sensory modalities, including the auditory and olfactory systems. However, little is known about how the brain integrates auditory and olfactory stimuli. In particular, the neural circuits governing how odors influence sound processing in the auditory cortex remain unexplored. Here, we investigated the mechanisms underlying auditory-olfactory integration using anatomical, electrophysiological, and optogenetic approaches. First, retrograde and anterograde viral tracing strategies revealed a direct projection from the piriform cortex to the auditory cortex, suggesting an anatomical substrate for odor modulation in auditory cortex. Next, using *in vivo* electrophysiological recordings of neuronal activity in the auditory cortex of awake mice, we found that odor stimuli modulate auditory cortical responses to sound. Finally, we used *in vivo* optogenetic manipulations during electrophysiology to demonstrate that odor modulation in auditory cortex, specifically odor enhancement of sound responses, depends on direct input from the piriform cortex. Together, our results identify a novel cortical circuit shaping odor modulation in the auditory cortex, shedding new light on neural mechanisms underlying auditory-olfactory integration.

Disclosures: **N.W. Vogler:** None. **R. Chen:** None. **A. Virkler:** None. **J.A. Gottfried:** None. **M.N. Geffen:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.28/E22

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

Support: Z01 DC000091

Title: Characterizing GABA's excitatory to inhibitory transition in mouse cochlear maturation

Authors: *H. J. BEAULAC[1], S. R. KITCHER[2], C. J. WEISZ[3];
[1]NIDCD, NIH, Bethesda, MD; [2]NIH, Bethesda, MD; [3]NIDCD, NIH / NIDCD, Bethesda, MD

Abstract: The mammalian cochlea responds to sound stimuli and regulates overall auditory sensitivity. Its innervation by afferent and efferent pathways forms the canonical central-peripheral auditory circuit. The central auditory system contains two separate efferent neuronal populations that project directly to the cochlea: the lateral olivocochlear (LOC) and medial olivocochlear (MOC) neurons. In the mature ear, MOC efferents directly synapse with the outer hair cells, the amplifying mechanosensory cells. MOC efferents release gamma-aminobutyric acid (GABA), which in the developing cochlea can activate presynaptic metabotropic $GABA_B$ receptors to downregulate efferent activity. Our lab has recently shown that GABA released from MOC efferents also acts on ionotropic $GABA_A$ receptors in type II spiral ganglion neurons. In the maturing brain, GABA activity at ionotropic receptors transitions from being primarily excitatory to inhibitory; the timing of a similar change in the cochlea is unknown. Therefore, we aimed to characterize the spatiotemporal changes in GABA activity within the mouse cochlea. To investigate how GABA released by MOC efferents affects spiral ganglion neuronal excitation, we evaluated changes in calcium activity, a proxy for neuronal excitation, in response to GABA. We injected AAV-GCamp7f (a fast calcium indicator) into the cochleae of C57BL/6J, Neurogenin1-CreERT2; tdTomato, and Bhlhb5-Cre; tdTomato mouse pups (both sexes) between postnatal day (P)0-2 for GCamp7f transduction in spiral ganglion neurons. In mice, response to sound stimuli is observed around P12. Therefore, cochleae were analyzed in age groups P4-7, P8-11, and P12-15. Using confocal imaging of calcium responses and Cre transgenic mouse lines to label MOC efferents and spiral ganglion afferent neurons, we observed higher GABA-evoked calcium activity in type II spiral ganglion neurons pre-hearing onset (P4-P7) compared to post-hearing onset (P15), suggesting that GABA is excitatory early in development before later becoming inhibitory. Our ongoing experiments will help inform us of GABA’s role in regulating GABAergic and glutamatergic activity in the maturing cochlea.

Disclosures: H.J. Beaulac: None. **S.R. Kitcher:** None. **C.J. Weisz:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.29/E23

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH grant 5R01MH123260

Title: Distinct electrophysiological properties of long-range GABAergic and Glutamatergic neurons from the lateral amygdala to the auditory cortex of the mouse

Authors: *A. BERTERO[1], A. J. APICELLA[2];
[1]UTSA, San Antonio, TX; [2]Neuroscience, developmental and regenerative Biol., Univ. of Texas at San Antonio, San Antonio, TX

Abstract: Differentiating between auditory signals of various emotional significance plays a crucial role in an individual's ability to thrive and excel in social interactions and survival. Multiple state of the art approaches have confirmed that the auditory cortex (AC) impacts auditory driven aversive behavior by conveying auditory information to the lateral amygdala (LA) through long-range excitatory glutamatergic, and more recently, GABAergic connections. In addition, the LA provides glutamatergic projections to the AC that are important to fear memory expression and are modified by associative fear learning. Here we test the hypothesis that the LA also sends long-range direct inhibitory inputs to the cortex. To address this fundamental question, we used anatomical and electrophysiological approaches, allowing us to directly assess the nature of GABAergic inputs from the LA to the AC in the mouse. Our findings highlight the existence of a previously undescribed long-range inhibitory pathway from the lateral amygdala to the auditory cortex via parvalbumin- and somatostatin-expressing (LAC-Parv, LAC-Som). Here we identified distinct electrophysiological properties for genetically defined long-range GABAergic neurons involved in the communication between the lateral amygdala and the cortex (**LAC-Parv inhibitory projections → AC neurons**; **LAC-Som inhibitory projections → AC neurons**) within the lateral-amygdala-cortical network. The existence of LAC-Glu, LAC-Parv, and LAC-Som opens several questions about their connectivity patterns and role in auditory processing. Are the lateral amygdala long-range excitatory glutamatergic and GABAergic neurons receiving different excitatory inputs from the medial geniculate body? Are LAC-Parv and LAC-Som receiving differential inputs from the cortical long-range excitatory/glutamatergic and inhibitory/GABAergic neurons? We will provide new results about the **Thalamic projections → LA neurons, AC inhibitory projections → LAC-Parv and LAC-Som neurons** and **AC excitatory projections → LAC-Parv and LAC-Som neurons** connectivity patterns involved in direct excitation/inhibition of LA principal neurons, or in local disinhibition, to shape the lateral amygdala response during perception and/or associative learning.

Disclosures: A. Bertero: None. **A.J. Apicella:** None.

Poster

PSTR023: Auditory Processing: Circuits, Synapses, and Neurotransmitters

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.30/E24

Topic: H.08. Learning and Memory

Title: Mecp2 regulates hearing loss and cognitive decline induced by repeated exposure to noise in adolescence

Authors: *K. JEONG[1,2], H.-I. IM[3,2];
[1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Div. of Bio-Medical Sci. &Technology, KIST School, Univ. of Sci. and Technol. (UST), Seoul, South Korea, Korea, Republic of; [3]Ctr. For Neurosci., Korea Inst. of Sci. & Technol., Seoul, Korea, Republic of

Abstract: Noise-induced hearing loss (NIHL) is the second most common sensorineural hearing loss after presbycusis, and the incidence of NIHL in adolescents has been increasing due to the increased use of portable audio devices. Recent studies have reported that NIHL can alter neural activity in various regions of the brain and cause not only hearing loss but also cognitive decline. However, the mechanism of how exposure to noise affects cognitive decline is not yet clear. MeCP2(Methyl-CpG Binding Protein 2) is an epigenetic regulator that activates or inhibits the transcription of target genes by binding to DNA, and is closely related to disorders such as Rett Syndrome and Alzheimer's disease, which have symptoms of both hearing loss and cognitive decline. Recent studies have reported an association between MeCP2 and cognitive or auditory functions, respectively. In addition, MeCP2 plays an important role in regulating synaptic plasticity and neural activity. Here, we confirmed the role of MeCP2 in hearing loss and cognitive decline induced by repeated noise exposure (NE) in adolescence. We established a NIHL model by exposing 3-week-old mice (CJ57/B6J) to 120 dB of noise for 3 hours per day for 3 weeks. We conducted ABR (Auditory Brainstem Response) and PPI (Pre-pulse Inhibition) tests at 1 week and 3 months after repeated NE, and confirmed that repeated NE causes hearing loss. In addition, it was observed that repeated NE caused a decline in cognitive function in NOR (Novel Object Recognition) and PA (Passive Avoidance) tests. To verify whether MeCP2 plays an important role in hearing loss and cognitive decline caused by repeated NE, we used immunochemical staining and Western blotting to determine changes in MeCP2 expression in the brain of an NIHL model. In our results, we found changes in MeCP2 expression levels in the medial geniculate nucleus (MGN) and hippocampus (dorsal/ventral) at 1 week and 3 months after NE. In addition, it was confirmed that the expression level of phosphorylated ribosomal protein S6 (rpS6), which reflects the level of neuronal activity, was changed in these areas. In the future, we plan to confirm the relationship between changes in MeCP2 and neuronal activity in the NHIL model by using Microelectrode Array (MEA) technology.

Disclosures: **K. Jeong:** None. **H. Im:** None.

Poster

PSTR024: Visual Cortex: Populations

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: /

Topic: D.06. Vision

Support: Foundation for Science and Technology (FCT) (2020.08995.BD)
National Science and Engineering Research Council of Canada (RGPIN-2020-05739)
Canadian Institutes of Health Research (PJT-156029 and PJT-180333)

Title: The endocannabinoid system in the visual cortex: perspectives for vision and beyond.

Authors: *C. MICAELO-FERNANDES[1], J.-F. BOUCHARD[1], M. PTITO[1,2];
[1]Sch. of Optometry, Univ. of Montreal, Montreal, QC, Canada; [2]Dept. of Neurosci., Univ. of Copenhagen, Copenhagen, Denmark

Abstract: The ECB system is expressed brain-wide and acts on the maintenance of an optimal excitatory-inhibitory balance by finely modulating synaptic activity and plasticity. However, disruptions in the ECB system have been linked to various neurodevelopmental and psychiatric disorders, including schizophrenia, autism, and chronic cannabis use. As a result of the significant cognitive and social impairments occasioned by the former, most of the anatomical and functional research on the ECB system has focused on higher brain regions such as the prefrontal cortex, overlooking structures involved in sensory processing.Nevertheless, all regions of the neocortex share the same neuronal subtypes and similar connectivity principles. Therefore, the visual system could facilitate the disclosure of the structural-functional relationships that underly not only the perceptual effects of cannabinoids, but also more complex behaviors mediated by the ECB system.To explore this hypothesis, we performed DAB immunohistochemical staining to analyze and compare the distribution of the CB1 receptor and FAAH enzyme across the striate and extrastriate cortices (V1, V2, V4, V5) of the vervet monkey. We also examined the relationship between these ECB proteins and key excitatory and inhibitory elements of the cortical microcircuit in more detail, by double and triple immunofluorescence.Our findings revealed laminar and regional differences in the expression of the ECB proteins. Namely, CB1R and FAAH expression was characterized by moderate to dense labeling of the supragranular and infragranular layers and weak labeling of layer 4, and their immunoreactivity increased with the cortical hierarchy, particularly in layers 2-3. CB1R and FAAH were mainly found in distinct cellular compartments, with the former being expressed in axons and the latter in somas and proximal dendrites. Co-localization analysis demonstrated the expression of FAAH in pyramidal cells and parvalbumin-expressing interneurons and allowed to identify CB1R/cholecystokinin-positive interneurons in layers 2-3.These results closely resemble data from other mammalian species and brain regions, suggesting some degree of modularity in the cortical expression of ECB proteins at the anatomical level and supporting the use of visual system as an experimental model for testing the effects of cannabinoids on brain function and behavior. To further validate this system, we are currently replicating this study in human brain specimens.

Disclosures: C. Micaelo-Fernandes: None. **J. Bouchard:** None. **M. Ptito:** None.

Poster

PSTR024: Visual Cortex: Populations

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.01/E25

Topic: D.06. Vision

Title: Spatial predictive coding in cortical neurons

Authors: *Q. ZHANG[1], A. L. GRACIAS[2], C. STRINGER[3], M. PACHITARIU[2];
[1]Janelia Res. Campus, Ashburn, VA; [2]Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA; [3]HHMI Janelia Res. Campus, Ashburn, VA

Abstract: Predictive coding is a theoretical framework for explaining how animals build internal models of their sensory environments. Predictive coding may either capture spatial or temporal relationships between sensory objects. While the original theory by Rao and Ballard 1999 described spatial predictive coding, most of the experimental data so far has been interpreted as evidence for temporal predictive coding. Here we directly tested whether the "surprise" neural population response to a novel stimulus is due to a spatial or a temporal internal model. We adopted two previously-developed paradigms to study predictive coding: one based on virtual-reality and one based on flashed static stimuli. In the virtual reality experiments, we trained mice to navigate through a linear corridor with a fixed sequence of stimuli for 5 days, while recording from large neural populations distributed over multiple visual cortical areas using calcium imaging with a two-photon mesoscope. After training, we performed several stimulus manipulations: 1) we replaced a stimulus with a gray wall, 2) we introduced a novel stimulus, 3) we altered the order of the stimuli or 4) we repeated a trained stimulus. The first and second manipulations induced a substantial "surprise" neural response, while the third and fourth ones did not. Thus, a surprise response only occurred if a new spatial, not temporal, pattern was introduced. We obtained similar results in the experiments with flashed stimuli in a separate cohort of mice. We conclude that primary sensory areas in mice build spatial rather than temporal models of sensory environments, and these internal models are reflected in the pattern-specific adaptation of neural responses over days.

Disclosures: Q. Zhang: None. **A.L. Gracias:** None. **C. Stringer:** None. **M. Pachitariu:** None.

Poster

PSTR024: Visual Cortex: Populations

Location: MCP Hall A

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Program #/Poster #: PSTR024.02/E26

Topic: D.06. Vision

Support: NIH Grant 1RF1MH128778-01
NIH Grant 1U01NS132267-01

Title: An edit-distance based metric represents neuronal morphologies and predicts their molecular identities

Authors: *S. WALLING-BELL, M. MALLORY, R. DALLEY, S. A. SORENSEN, U. SÜMBÜL;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Despite significant research over decades, there is no consensus on how to represent and compare neuronal morphology. This limits our ability to study them in the context of cell types in both unimodal and multimodal settings. Here, we develop a new method to compare neuronal arbors, based on the cost of editing morphologies, that defines a mathematical distance metric. We first develop a metric to compare individual branches. This metric can compare the shapes of the branches, beyond their overall lengths and orientations. We then extend this to a distance metric on whole arbors that takes the branching patterns into account and is robust against the addition and removal of short branches at arbitrary locations on the arbors. We apply our method to compare different traces of the same neuron (e.g., manual vs automated) and on a set of somatostatin-expressing cortical neurons for which transcriptomic profiles are available. We show that the method can identify the differences between different traces of a given neuron, demonstrating its utility as a diagnostic tool. We also show the applicability of the method to the analysis of neuronal morphologies. The distances computed by the method convey a sense of distance in the mathematical sense. We show these can be used to predict other aspects of the phenotype in addition to summarizing the morphology.

Disclosures: S. Walling-Bell: None. **M. Mallory:** None. **R. Dalley:** None. **S.A. Sorensen:** None. **U. Sümbül:** None.

Poster

PSTR024: Visual Cortex: Populations

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.03/E27

Topic: D.06. Vision

Title: Video reconstruction from mouse visual cortex activity

Authors: *J. BAUER[1,2], T. W. MARGRIE[3], C. CLOPATH[4,5];
[1]Sainsbury Wellcome Ctr., UCL, London, United Kingdom; [2]Imperial College London, London, United Kingdom; [3]Sainsbury Wellcome Ctr., London, United Kingdom; [4]Imperial Col. London, London, United Kingdom; [5]Sainsbury Wellcome Centre, UCL, London, United Kingdom

Abstract: Vision reconstruction from brain activity has the potential to give us unprecedented insight into the perceptual experience of animals and how the brain represents visual information. Over the past decade, there have been considerable advances in reconstructing images and videos from human fMRI recordings. Less attention has been given to image reconstruction from non-human brains despite the availability of large-scale single-cell resolution recording techniques. Recently, deep nonlinear neural networks have been used to reconstruct static images from monkey V4 extracellular recordings, with promising results. Here,

we present a method for reconstruction of 10-second movie clips at 30 Hz using two-photon calcium imaging data from mouse V1. We demonstrate high-quality video reconstructions, approaching the spatial and temporal limits of the mouse visual system. We achieve this using iterative optimization of the input videos via gradient descent through a state-of-the-art dynamic neural encoding model from the Sensorium 2023 competition. We show that for high-quality reconstructions, the number of neurons in the dataset and averaging the reconstructed videos from multiple models is critical.

Disclosures: J. Bauer: None. **T.W. Margrie:** None. **C. Clopath:** None.

Poster

PSTR024: Visual Cortex: Populations

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.04/E28

Topic: D.06. Vision

Support: EIC grant HYPERSTIM No101071015
FWO grant G0D6520N
IDN grant KU IDN/19/043

Title: Effects of epicranial direct current stimulation on orientation tuning in macaque primary visual cortex

Authors: *L. MERKEN[1], M. SCHELLES[2], P. JANSSEN[1];
[1]KU Leuven, Leuven, Belgium; [2]Electrical Engin., KU Leuven, Leuven, Belgium

Abstract: Transcranial Direct Current Stimulation (tDCS) is a non-invasive technique to modify cortical excitability, which has been proposed as an intervention for various neurological disorders. However, due to the variable results that have been reported with tDCS, it is crucial to understand the effects of this technique at the neuronal level. We applied 0.5 mA anodal epicranial DCS (eDCS) and simultaneously recorded multi-unit activity from 100 chronically implanted flexible electrodes in the primary visual cortex of an awake rhesus monkey. Epicranial stimulation avoids shunting of the current through the skin and inadvertent stimulation of peripheral nerves. We used custom-built spiral-shaped platinum eDCS electrodes with an outer diameter of 5 mm which were placed on the skull above primary visual cortex and contralateral somatosensory cortex. The monkey performed a passive fixation task while we presented bars of 1.5 degrees in 6 different orientations and at different positions in and outside the receptive field (receptive fields ranged from 0 to 4 visual degrees eccentricity). EDCS was applied in a block design of 1 min eDCS followed by a 10 min no-eDCS block which was repeated 4 to 13 times in a single recording session. In one session, 78 out of 100 channels were significantly visually responsive (left-sided Wilcoxon rank sum test comparing pre- and post-stimulus onset periods of 150 ms, $p < 0.05$). We calculated the orientation tuning curve as the slope of the ranked net responses to the six orientations at the preferred position (the center of the RF). EDCS

significantly improved the orientation tuning since the slope of the average tuning curve became significantly steeper during eDCS in comparison to no-eDCS (eDCS: slope=-6.86, 95% CI [-5.94, -7.78]; no-eDCS: b=-2.46, 95% CI [-1.75, -3.18]). Interestingly, eDCS also modulated the orientation tuning at non-preferred positions. More than half of the channels (52/100) showed a significant orientation tuning during eDCS at positions which were not responsive in the absence of eDCS (eDCS: b=-5.44, 95% CI [-4.45, -6.44]; no-eDCS: b=-0.26, 95% CI [-0.01, -0.51]). These results demonstrate that eDCS exerts two types of effects on orientation tuning in the primary visual cortex: a sharpening of the tuning at the center of the RF and the emergence of tuned responses at positions outside the RF center.

Disclosures: **L. Merken:** None. **M. Schelles:** None. **P. Janssen:** None.

Poster

PSTR024: Visual Cortex: Populations

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.05/E29

Topic: D.06. Vision

Support: NIH Grant R00EY028612
NIH Grant R01NS120850

Title: Coordination of population spiking variability in visual cortex is layer-, area-, and timescale dependent.

Authors: *D. DENMAN[1], J. SANTIAGO MORENO[1], J. L. HICKMAN[2];
[1]Univ. of Colorado Anschutz, Aurora, CO; [2]Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: Sensory stimuli are represented by the joint activity of large populations of neurons across brain areas. In most systems, including the mammalian visual system, this evoked activity is variable, even in response to the same external input. Because that variability is not independent between neurons, it has the potential to improve or degrade the amount of sensory information in the population response. How visual information scales with population size in visual cortical and thalamic populations, and whether the coordination of variability in large populations affects information, remains an open empirical question. Here, we use Neuropixels to simultaneously record tens to hundreds of single neurons in a series of interconnected populations: across the layers of primary visual cortex (V1) and lateral geniculate nucleus (LGN) of awake mice in response to repeated external inputs (visual stimuli) and direct internal inputs (electrical stimuli). Using this data, we extensively characterized the pairwise correlations in responses - both signal and noise correlations - and estimate population information at timescale ranging from single to hundreds of milliseconds using supervised decoding as a proxy for information. We found that noise correlation was dependent on signal correlation as well as the timescale of the measurement and the response, and quantify this dependence. We assess the

effect of correlated variability across timescales of various subsets within the visual circuit, constraining population by cell type and circuit location (e.g, cortical layer or unsupervised discovery of coding clusters from within the total recorded population). We relate correlated variability in populations to overall population latent structure. Finally, we contrast the usefulness of correlated variability in such populations when that variability arises from distinct retinal input (i.e., distinct visual stimuli) compared to direct excitation of cortex using electrical stimulation.

Disclosures: D. Denman: None. **J. Santiago Moreno:** None. **J.L. Hickman:** None.

Poster

PSTR024: Visual Cortex: Populations

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Program #/Poster #: PSTR024.06/E30

Topic: D.06. Vision

Support: NS007292
R35NS111562

Title: The role of layer 1 NDNF+ interneurons in visual learning

Authors: *M. SHANLEY[1], G. TURRIGIANO[2];
[1]Brandeis Univ., Watertown, MA; [2]Dept of Biol., Brandeis Univ., Waltham, MA

Abstract: Inhibitory neurons in layer 1 of the cortex, identified by Neuron Derived Neurotrophic Factor (NDNF), receive inputs from various cortical and subcortical regions. In the primary visual cortex, these cells have been shown to respond strongly to important sensory stimuli while modulating the local cortical circuit based on internal and external cues. However, little is currently understood about the role of these cells in learning during the visual critical period and adulthood. Rodents are opportunistic omnivores and enthusiastically hunt crickets in a laboratory setting when motivated by food restriction. Importantly, we and others have shown that cricket hunting ability is vision-dependent, improves with experience, and induces plasticity in the primary visual cortex of adolescent rodents. The cricket hunting paradigm allows for the investigation of visual learning and the underlying circuitry in a controlled but ethologically relevant context. We have shown, using slice electrophysiology, that NDNF+ neurons exhibit an increase in intrinsic excitability in animals that have successfully learned to capture crickets, suggesting that they are important modulators of the circuit to improve visual detection of a cricket. To further investigate the role of NDNF+ neurons in visual learning, we used chemogenetic manipulations to activate and inhibit NDNF+ neurons at various stages of the learning process and found that inhibition of NDNF+ neurons enhances early learning, demonstrated by a reduction in the time to capture the cricket. Since inhibiting NDNF+ neurons decreases the time to capture a cricket, and previous studies show an association with NDNF+ activity and attention, NDNF+ neuron activity might be working as a break to allow the circuit to

remain flexible while learning is occurring. This may help shape the selectivity of the circuit towards the most relevant visual stimuli, rather than "locking in" on the first salient stimulus that the mouse encounters.

Disclosures: **M. Shanley:** None. **G. Turrigiano:** None.

Poster

PSTR024: Visual Cortex: Populations

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Topic: D.06. Vision

Support: T32-GM149364
NIH R01 EY035896
Simons Collaboration on the Global Brain 542999

Title: Assessing the role of the macaque pulvinar in mediating communication between visual cortical areas

Authors: ***A. XU**[1], A. I. JASPER[1], A. KOHN[1,2,3];
[1]Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY; [2]Department of Systems and Computational Biology, Albert Einstein College of Medicine, Bronx, NY; [3]Department of Ophthalmology Visual Sciences, Albert Einstein College of Medicine, Bronx, NY

Abstract: Understanding inter-areal communication is central to understanding brain function, which relies on activity distributed across multiple regions. Recent work has shown that cortical areas interact through a communication subspace—a low-dimensional mapping of population activity patterns that defines which activity is relayed between areas and which remains private within the source area. In addition to direct cortico-cortical (CC) connections, visual cortical areas may also communicate via the pulvinar—a higher order thalamic nucleus. Though this cortico-pulvino-cortical (CPC) pathway may be an important additional pathway for signaling between cortical areas, it has received little experimental exploration. By simultaneously recording population spiking activity in the pulvinar and visual areas V1 and V2 of anesthetized macaque monkeys, we sought to compare CC and CP signaling, leveraging the communication subspace framework to investigate how each source area communicates with each target area. Additionally, we probed how pharmacological inactivation of the pulvinar altered cortical responses and inter-areal signaling.
We fit multivariate regression models to predict the trial-to-trial fluctuations of activity in one area using the fluctuations of population activity in another. Cortical activity in a source area was predictive of pulvinar activity to a similar extent as its usefulness for explaining activity in a target cortical area. The mapping relating cortical to pulvinar activity was low dimensional, indicating that CP interactions utilized a communication subspace, as previously found for CC

interactions. We tested whether the signals relayed from a source cortical area to the pulvinar and a target cortical area were similar and found that CP and CC subspaces relied on different patterns of source activity.
Since CC and CP pathways relayed distinct patterns of activity, we explored the importance of the CPC pathway to cortical activity within and across areas. Muscimol injections in the pulvinar effectively silenced local activity but did not strongly affect evoked or spontaneous activity in either V1 or V2. However, the orientation selectivity of both areas became broader, suggesting that pulvinar input may influence cortical selectivity. Both the predictive performance and dimensionality of V1-V2 regression models decreased following inactivation, suggesting a change in cortico-cortical interactions.
Our results are consistent with proposals that the CPC represents a distinct pathway for relaying signals between cortical areas.

Disclosures: **A. Xu:** None. **A.I. Jasper:** None. **A. Kohn:** None.

Poster

PSTR024: Visual Cortex: Populations

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DARPPA grant DARPA-NESD-N66001-19-C-4020

Title: Fast nonlinear neural population dynamics measured with a genetically-encoded voltage indicator from behaving macaque V1

Authors: *Y. CHEN[1], **J. ZHOU**[2], M. P. WHITMIRE[1], P. K. TAN[3], V. A. PIERIBONE[4], W. S. GEISLER[5], E. SEIDEMANN[6];
[1]Univ. of Texas at Austin, Austin, TX; [2]Flatiron institute, center for computational neuroscience, NYC, NY, ; [3]Univ. Of Texas At Austin Inst. For Neurosci., Austin, TX; [4]Yale Univ., New Haven, CT; [5]Univ. Texas Austin, Austin, TX; [6]The Univ. of Texas At Austin, Austin, TX

Abstract: Genetically encoded fluorescent voltage indicators (GEVIs) can measure millisecond-scale neural responses with cell-type specificity in behaving animals. However, until now, GEVI imaging has not been used successfully in non-human primates, which are a powerful animal model for human perception, cognition and motor control. Here, we used viral vectors to chronically express the GEVI pACE (Kannan et al, Science, 2022) in excitatory V1 neurons in two macaque monkeys. We then used widefield imaging to measure GEVI dynamics in response to flashed visual stimuli with diverse temporal waveforms and contrasts. We compared these

GEVI responses to signals measured from excitatory V1 neurons using the genetically-encoded calcium indicator GCaMP6f in response to identical stimuli. Our goals were twofold. First, to characterize the GEVI signals and develop a quantitative model that predicts the nonlinear GEVI response dynamics to stimuli with arbitrary temporal waveforms and contrasts. Second, to quantitatively compare the GEVI and GCaMP responses in order to test the hypothesis that GEVI signals reflect locally summed membrane potentials while GCaMP signals reflect summed spiking activity. We obtained high quality GEVI responses that precisely track the fast and nonlinear dynamics of V1 population responses. When compared to GCaMP, the GEVI captures the fine-detail dynamics of the response, tracks higher stimulus temporal frequencies, and responds to lower stimulus contrasts. These GEVI results are qualitatively similar to the dynamics of V1 signals measured with synthetic voltage sensitive dyes (Sit et al, Neuron, 2009), a signal that has been shown to reflect the locally pooled membrane potential (Chen et al, J Neurophysiol, 2012). We find that a simple delayed normalization model with distinct temporal filters for the numerator and normalization denominator can account for the observed nonlinear GEVI responses. The same model with a slower and more sluggish linear filter can account for the GCaMP data. Overall, our results are consistent with the hypothesis that GEVI signals reflect the dynamics of summed membrane potential, thus opening the door for a new and powerful class of experiments in behaving primates.

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Poster

PSTR024: Visual Cortex: Populations

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.09/E33

Topic: D.06. Vision

Title: Temporal information of subsecond sensory stimuli is encoded by high dimensional population vectors in primary visual cortex

Authors: *S. POST[1], W. MOL[2], N. RAHMATULLAH[3], A. GOEL[4];
[1]UC Riverside, Riverside, CA; [2]Univ. of California Riverside, Riverside, CA; [3]Univ. of California, Riverside, Riverside, CA; [4]Psychology, UCR, Riverside, CA

Abstract: Temporal processing of sensory stimuli in the millisecond-to-second scale is critical to prediction and survival, such as in a prey anticipating not only where a charging predator will go but also when the predator will arrive at that location. However, it is not clear: if 1) temporal information is generated in higher order or lower order areas of the brain, and 2) if temporal information is encoded intrinsically by neural networks or if it is generated by specialized neural activity, i.e. dedicated mechanisms.
To elucidate these questions, we recorded neural activity in primary visual cortex (V1) using 2-photon Ca2+ imaging as mice (male and female) performed a goal directed sensory

discrimination task, in which patterns of subsecond stimuli differed only in their temporal profiles. We found that temporal information was encoded in the changing population vector (the trajectory) of the network and that the space between these trajectories was maximized in learned sessions. Further, we validated these results against machine learners and found that they converged to the same solutions as our calculations of state space divergence. These results validate a prominent model of timing which proposes that temporal information is encoded intrinsically and requires no specialized neural mechanisms.
Additionally, we isolated any cells in our recordings that were reminiscent of oscillatory or ramping activity, activity indicative of two competing models of timing that propose that temporal encoding relies upon specialized neural activity. We found that neural decoding of these specialized populations was equivalent to decoding of non-specialized populations, both at the single unit and population level. We further found that activity in oscillatory and ramping populations were in fact aspects of the entire population's trajectory. Our results suggest that 1) temporal information can be generated by lower-order sensory areas; and 2) that temporal information can be intrinsically generated by population dynamics and does not require specialized mechanisms to do so.

Disclosures: **S. Post:** None. **W. Mol:** None. **N. Rahmatullah:** None. **A. Goel:** None.

Poster

PSTR024: Visual Cortex: Populations

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Topic: D.06. Vision

Support: National Natural Science Foundation of China 32271079
National Natural Science Foundation of China 31625012

Title: Binocular-rivalry-like activity observed with 2-photon calcium imaging in anesthetized macaque V1

Authors: *J. WANG, R. ZHANG, X. CAI, H. D. LU;
State Key Lab. of Cognitive Neurosci. and Learning, Beijing, 100091, China

Abstract: Objective Binocular rivalry (BR) occurs when incompatible visual images are presented to each of the two eyes. Rather than forming a uniform percept, the two stimuli rival for exclusive dominance, which results in a continuous perceptual alternation. Despite many years of research, the specific role of primary visual cortex (V1) in BR process remains unclear. By measuring the activity of populations of V1 neurons, we aim to gain more insights into how rivalrous stimuli were processed in V1. **Methods** V1 neurons in 3 macaques were infected by AAV-GCaMP6s virus. Dichoptic patches of orthogonal sinewave gratings were presented to anesthetized macaques to provide either binocularly inconsistent (BR conditions) or consistent (control conditions) visual inputs. Activity of hundreds of superficial V1 neurons was recorded

simultaneously using two-photon calcium imaging techniques. **Results** (1) Compared to their spontaneous activity, 81% neurons (1361/1681) exhibited larger amplitude of fluctuations when the BR stimuli were presented (paired t-test, $p<0.05$). The fluctuation amplitude varied from neuron to neuron and formed a continuous unimodal distribution. (2) For a pair of dichoptic BR stimuli, neurons that were selective to one of these patterns had the strongest fluctuation. Accordingly, monocular neurons usually had greater fluctuations than binocular neurons do. (3) Neurons with similar eye or orientation preference tended to synchronize under BR conditions. For neurons their preferred orientation was presented to the non-preferred eye (i.e., non-preferred orientation was presented to preferred eye), their synchronization within eye network was dominant. (4) The dominance duration distribution could be fitted by a gamma distribution and the alternation patterns were significantly modulated by stimuli strength, both of which were consistent with BR perception. **Conclusion** (1) Rivalry-like activity exists in anesthetized macaque V1 at neuronal level. (2) The majority of V1 neurons participate, in various degrees, in such a rivalry-like activity.

Disclosures: **J. Wang:** None. **R. Zhang:** None. **X. Cai:** None. **H.D. Lu:** None.

Poster

PSTR024: Visual Cortex: Populations

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Program #/Poster #: PSTR024.11/E35

Topic: D.06. Vision

Support: KNAW Grant

Title: Population receptive field size across cortical depth along the visual hierarchy

Authors: *M. BITTENCOURT[1,2], M. DAGHLIAN[2,1], R. RENKEN[1], S. O. DUMOULIN[2], F. W. CORNELISSEN[1];
[1]Univ. Med. Ctr. Groningen, Groningen, Netherlands; [2]Spinoza Ctr. for Neuroimaging, Amsterdam, Netherlands

Abstract: In the visual cortex, population receptive field (pRF) size increases both with eccentricity and when moving up along the visual hierarchy. Previous functional magnetic resonance imaging (fMRI) and neurophysiology studies found that in the primary visual cortex (V1), pRF size varies across cortical depth according to a U-shaped function, with the smallest pRF sizes in central layers. This U-shaped pattern is thought to reflect the hierarchical information flow across cortical depth, where the information arrives in central layers and is further processed in superficial and deeper layers. However, it is still unknown how pRF properties are organized across cortical depth in later visual areas. Here, we use population receptive field modeling at ultra-high field (7T) functional MRI to investigate pRF size variation across cortical depth and along the visual hierarchy (i.e. V1-hV4, LO-1 and LO-2) at sub-millimeter resolution (0.8mm isotropic). Functional data preprocessing included thermal

denoising, susceptibility distortion correction, motion correction and high-pass filtering. Both anatomical and functional data were upsampled to 0.4mm isotropic resolution. Anatomical images were co-registered to functional images, segmented into gray matter, and divided into eight equivolumetric cortical surface layers. Our results show that in V1, pRF size follows the expected U-shaped function with cortical depth. In V2 and beyond, our preliminary results did not reveal a clear U-shaped function potentially suggesting a different association between pRF size and cortical depth. This study brings new evidence on the laminar organization of pRF properties along the visual hierarchy that require further investigation.

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Poster

PSTR024: Visual Cortex: Populations

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Program #/Poster #: PSTR024.12/E36

Topic: D.06. Vision

Support: CIHR
RRSV

Title: Diverse Neuronal Responses to Visual Precision in Cat Area 21a

Authors: ***N. CORTES**[1], L. IKAN[1], C. F. CASANOVA[2];
[1]Univ. de Montréal, Montreal, QC, Canada; [2]Sch. of Optometry, Univ. de Montéal, Montreal, QC, Canada

Abstract: Our research investigates the impact of visual stimuli precision on orientation processing in higher cortical areas. Specifically, we examined cortical area 21a in cats, often considered the equivalent of primate area V4 within the hierarchical organization of visual processing. 'Motion Clouds' (MC), pseudo-natural stimuli, were used to explore orientation precision's effects on neuronal responses. MC precision is governed by four parameters: the orientation, the spatial frequency (SF), B_{θ}, and B_{sf}. We analyzed responses from 411 neurons in area 21a, seeking patterns in orientation precision processing. Our findings reveal a large range of neuronal responses. A significant proportion of neurons (56%) exhibited peak discharge at the highest precision levels, indicating a preference for finely tuned stimuli. In contrast, 33% displayed maximum discharge at lower precision levels. Within the high-precision group, there were varied responses: 39% were highly sensitive to the highest precision, 16% showed a gradual decreasing activation with reduced precision, and 44% had increased firing rates at two precision levels. The lower precision group also presented variability: 60% of neurons had peak activation at sub-maximal precision, while 40% increased activation towards lower precision. These results highlight a broad spectrum of precision response profiles in higher cortical visual areas and suggest a role for the cortical ventral stream in precision processing.

Theoretical analysis of MC textures shows that as the precision of the images increases, their complexity decreases. This suggests that across the visual hierarchy, precision coding should diminish in response to textures with higher precision and increase for textures with lower precision. Thus, the visual system may utilize reduced precision to produce higher complexity coding, revealing how the cortex may use precision information to influence visual perception. Our study contributes to the understanding of cortical visual processing, emphasizing the complexity and variability in neuronal response to visual precision. Supp: CIHR and RRSV to CC.

Disclosures: **N. Cortes:** None. **L. Ikan:** None. **C.F. Casanova:** None.

Poster

PSTR024: Visual Cortex: Populations

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Topic: D.06. Vision

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5-T32-EY-021462-12

Title: Optogenetic silencing of PV and SST cells disrupts disparity tuning in excitatory cells

Authors: *M. C. SEVERSON[1], J. M. SAMONDS[2], N. J. PRIEBE[3];
[1]Inst. For Neurosci., Univ. Of Texas At Austin, Austin, TX; [2]Ctr. for Learning and Memory, Univ. of Texas At Austin, Austin, TX; [3]Neurosci., Univ. Texas, Austin, Austin, TX

Abstract: Neurons in primary visual cortex (V1) are the first in the visual pathway to integrate input from both eyes. To use this information, the brain must solve the stereo correspondence problem of determining which points in one retinal image correspond to the same points in the other retinal image. The disparity energy model (Ohzawa et al., 1990) describes the integration of signals from both eyes, but it does not fully address the mechanism behind how neurons in the brain solve stereo matching. Neurons solving the correspondence problem must be doing more than simply integrating left and right eye input, they must also be enhancing correct matches and suppressing false matches. Inhibitory neurons would be ideal candidates for suppressing false matches because they integrate information from excitatory cells and can, in turn, selectively inhibit those responses. To determine the contributions of two classes of inhibitory neurons, parvalbumin-expressing (PV) and somatostatin-expressing (SST), to disparity tuning in excitatory cells, we sought to measure the impact of inhibitory cell suppression on excitatory cell disparity tuning using optogenetics. Using combined two-photon calcium imaging and optogenetics, we show that silencing PV and SST inhibitory cells affects disparity tuning differentially. The suppression of SST cells resulted in increased responses of excitatory cells (60% higher on average) to non-preferred disparities while the suppression of PV cells resulted in about half as much disinhibition. Suppression of PV cells resulted in increased excitatory cell

responses by 30% on average. Overall, disparity tuning was broadened with suppression of both SST and PV cells, though more broadening was seen with SST suppression. The differential effects of suppressing these classes of inhibitory neurons suggests that they play distinct roles in solving the stereo correspondence problem. We hypothesize that PV cells play a critical role in suppressing false matches, whereas SST cells play a role in sculpting disparity tuning to enhance correct matches. Taken together, our findings illustrate how integration by inhibitory neurons plays an essential role in binocular vision by helping to solve the stereo correspondence problem.

Disclosures: M.C. Severson: None. **J.M. Samonds:** None. **N.J. Priebe:** None.

Poster

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Program #/Poster #: PSTR024.14/E38

Topic: D.06. Vision

Support: ZIAMH002966
Wu Tsai Neurosciences Institute

Title: Orientation selectivity of mouse superior colliculus modeled with center-surround receptive fields

Authors: *A. KUO[1,2], J. L. GARDNER[1], E. P. MERRIAM[3];
[1]Psychology, Stanford Univ., Stanford, CA; [2]Neurosciences Interdepartmental Program, Stanford University, Stanford, CA; [3]NIMH/LBC, NIH, Natl. Inst. of Mental Hlth. (NIMH), Washington, DC

Abstract: Can a neural population be selective for properties of a stimulus none of its constituent neurons are selective for? Foundational single unit physiology experiments show that orientation selective (OS) neurons emerge in primate V1 but are not present in subcortical structures such as LGN or superior colliculus (SC). Accordingly, a single neuron perspective suggests linear readout of stimulus orientation from population responses should be possible from V1, but not LGN or SC. Here we ask whether Ca2+ imaging of population activity from mouse SC, widely reported in the literature to be OS, necessarily implies that single SC units have V1-like receptive fields (RFs) with elongated subfields. We simulated neural responses based on a study (Liang et al., 2023, Nat Commun 14:4756) that made thorough measurements from mouse superficial SC using a battery of stimuli varying in orientation (0, 30, 60, 90, 120, 150°), SF (0.01-0.32 cycles/°), size (radii: 19, 29, 40°), and shape. We simulated both V1-like and center-surround (CS) RFs at the single unit and population scale. RF sizes (~50-250 deg2) and spatial frequency (SF) selectivity (0.01-0.32 cycles/°) were based on prior measurements. Our simulations showed that V1-like and CS RFs both produced similar patterns of population orientation tuning that depended on both aperture shape and size. At the population scale for both RF types, we demonstrated a shift in orientation selectivity from a radial to tangential bias as

stimulus SF increases, reproducing empirical findings. For single model units, patterns of CS orientation preference closely matched those measured from single unit SC neurons, which depended on location along the aperture, as Liang et al. describe. Our model provides a unified explanation of edge-related orientation selectivity detailed in Liang et al. and suggests that empirically measured orientation selectivity from SC populations need not imply V1-like RFs in SC. Instead, SF selectivity of single neurons may confer selectivity for orientation to the population. We do not claim this result precludes the existence of V1-like RFs in the Liang data or in other mouse SC data; rather, our model simulations provide a tool to experimenters for determining RF properties sufficient to explain population responses. Broadly, our results demonstrate the population response can be greater than the sum of its parts by exhibiting selectivity none of its constituent neurons show, which in principle could be read out by downstream perceptual and motor systems.

Disclosures: **A. Kuo:** None. **J.L. Gardner:** None. **E.P. Merriam:** None.

Poster

PSTR024: Visual Cortex: Populations

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Topic: D.06. Vision

Support: NIH Grant NS130475
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Carney Innovation Fund

Title: Simultaneous recording of large neural populations across multiple visual areas in macaque temporal cortex

Authors: *R. L. MILLER[1], D. L. SHEINBERG[2];
[1]Brown Univ., Providence, RI; [2]Neurosci., Brown Univ., Providence, RI

Abstract: Evaluating the responsiveness of large numbers (>100) of neurons in deep targets (>20 mm) in the non-human primate brain has only recently become truly feasible with Neuropixels probes. Offering 4416 recording sites spaced over a 45 mm shank, these probes provide an opportunity to study how complex populations of neurons work together to, for example, represent the visual world. For our studies, we developed an innovative chamber and electrode drive system to place this probe deep in the macaque brain. Using structural fMRI, we designed a combination of 3D-printed and off-the-shelf parts to drive the probe into the brain, with access to multiple sensory areas along a vertical trajectory. Our primary target was the superior temporal sulcus (STS), which includes cells with sensitivity to complex visual objects and dynamic scenes. The system provides sub-micron precision for multi-hour stable recordings for less than $500, including the custom fit implanted chamber. Typically when using probes with small numbers of channels, stimuli are catered for the expected sensitivities in the region.

Using a Neuropixels probe and sampling over a large range of depths (20+ mm) avoids this inherent bias and allows the opportunity for identifying unexpected contributions from neurons in adjacent regions. We have recorded the simultaneous activity of large populations of neurons across both banks of the STS in response to a battery of stimuli including static images and video clips.

Disclosures: R.L. Miller: None. **D.L. Sheinberg:** None.

Poster

PSTR024: Visual Cortex: Populations

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.16/E40

Topic: D.06. Vision

Support: HMBA

Title: Evolution of Cell Types in the Mammalian Primary Visual Cortex

Authors: *M. T. SCHMITZ[1], N. JOHANSEN[2], Y. FU[3], I. KAPEN[3], A. A. DE SOUSA[4], M. WIRTHLIN[5], J. PUCKETT[6], A. GARCIA[7], J. T. GOLDY[8], A. T. CHAKKA[3], S.-L. DING[6], C. M. SOBIESKI[9], K. T. JAMES[3], R. A. FERRER[10], R. T. CHAKRABARTY[3], B. T. NGUY[3], A. C. HALLEY[11], G. K. WILKERSON[12], D. FITZPATRICK[13], L. A. KRUBITZER[14], J. J. PADBERG[15], G. BALMUS[16], C. SHERWOOD[17], E. G. BARRETT[18], B. P. LEVI[2], K. A. SMITH[3], E. LEIN[2], T. BAKKEN[6];
[1]Evolutionary Genomics, Allen Inst. for Brain Sci., Seattle, WA; [2]Human Cell Types, Allen Inst. for Brain Sci., Seattle, WA; [3]Allen Inst., Seattle, WA; [4]Col. of Vet. Med., Auburn Univ., Auburn, AL; [5]Allen Inst. for Brain Sci., Allen Inst. for Brain Sci., Seattle, WA; [6]Allen Inst. for Brain Sci., Seattle, WA; [7]Human Cell Types, Allen Inst., Seattle, WA; [8]BiCore, Allen Inst. For Brain Sci., Seattle, WA; [9]Human Cell Types, Allen Inst., Charleston, WV; [10]Basic Biobehavioral and Psychological Sci. Br., Natl. Cancer Inst., Bethesda, MD; [11]Ctr. for Neurosci., Univ. of California Davis, Davis, CA; [12]Pathology and Lab. Sci., Univ. of North Carolina at Chapel Hill, New Hill, NC; [13]Max Planck Florida Inst., Jupiter, FL; [14]UC Davis, Davis, CA; [15]Dept. of Biol., Univ. of Central Arkansas, Conway, AR; [16]Cambridge Univ., Cambridge, United Kingdom; [17]George Washington Univ., Washington, DC; [18]Pharmacol., Lovelace Biomed., Albuquerque, NM

Abstract: The primary visual cortex (V1C) is responsible for receiving visual input to the cortex from the retina via the thalamus and passing information to secondary processing areas by embedding edge orientation, color, stereopsis and other features. V1C is known to be highly specialized in its cytoarchitecture, cell type proportions and is known to contain many area-specific cell types in the human brain. We used simultaneous single nucleus RNA and ATAC sequencing to sample V1C in 14 mammalian species, spanning primates, rodentia, laurasiatheria, xenarthra and marsupialia. We found that the cell types in V1C are highly specialized relative to

other areas of the cortex across the many species in our sample set. We also provide preliminary differences in gene expression and cell composition between subregions of V1C. Finally, we overview the landscape of cis-regulatory element conservation across diverse species and discuss the path forward for leveraging evolutionary sequence exploration to understand cis-regulatory element function in cortical cell types.

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Poster

PSTR024: Visual Cortex: Populations

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.17/F1

Topic: D.06. Vision

Support: NIH Grant EY025102

Title: Excitatory and inhibitory neuron comparison in marmoset area MT

Authors: *J. J. PATTADKAL[1], B. V. ZEMELMAN[2], N. J. PRIEBE[3];
[1]Neurosci., The Univ. of Texas at Austin, Austin, TX; [2]The Univ. of Texas at Austin, Austin, TX; [3]Neurosci., Univ. Texas, Austin, Austin, TX

Abstract: Cortical circuits are composed of many excitatory and inhibitory cell classes. The role of inhibitory interneurons in circuit computations, particularly in the primate cortex, has remained elusive, due to lack of targeted approaches to record from these cell types. We have previously developed viral strategies to tag different inhibitory classes in the primate brain (Mehta et al, 2019). Using these tools, we now ask whether the functional properties of inhibitory and excitatory neurons in awake marmoset cortex are shared or distinct, using two-photon calcium imaging of cortical area MT. We simultaneously recorded from both excitatory and inhibitory populations using calcium indicator GCaMP. The inhibitory cells were identified using a tdTomato expression driven by the inhibitory promoter h56D. We performed a number of comparisons and found a striking similarity in the responses of excitatory and inhibitory neurons. We first compared selectivity for visual motion across excitatory and inhibitory populations. Both excitatory and inhibitory populations in marmoset MT exhibited similar selectivity for motion direction (median direction index for E cells: 0.38, for I cells: 0.36). We next compared the whether the magnitude of spontaneous responses differed across both populations. The cell types also did not differ in spontaneous responses. We estimated the local

connectivity of the two populations by analyzing the relation between the cell's tuning to its neighboring population. The correlation of cell's tuning to its local neighborhood was similar across both populations, with the correlation declining at distances longer than ~150 microns. Lastly, we compared the relation between neuronal responses and behavioral responses across cell types. We measured ocular following eye movements in response to dots motion in marmosets while recording activity from area MT. Population representation of motion signal across MT was related to direction of eye movements across motion directions. Noise in ocular following responses within a condition was however not found to be related to noise in population representation of motion for that condition. No differences were found between the contributions of excitatory and inhibitory populations to ocular following behavior. In sum, our results suggest that inhibitory neurons in primate cortex do not differ drastically in their response characteristics from excitatory cells, and their contributions to circuit functions may instead rely on their co-tuning with excitatory cells.

Disclosures: J.J. Pattadkal: None. **B.V. Zemelman:** None. **N.J. Priebe:** None.

Poster

PSTR024: Visual Cortex: Populations

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Program #/Poster #: PSTR024.18/F2

Topic: D.06. Vision

Support: National Natural Science Foundation of China (62171254)
National Key Research and Development Program of China (2023YFC3402600)

Title: Visual predictive coding by high throughput neural computation of whole cerebral cortex

Authors: *J. XIE, G. XIAO, J. WU, Q. DAI;
Tsinghua Univ., Beijing, China

Abstract: The visual prediction encoding is realized through bidirectional multilevel information processing pathways in the neural system across various brain regions. Acquiring high throughput biological visual prediction data is of paramount importance for deciphering the working mechanisms of visual prediction and constructing novel artificial intelligence networks for cognitive simulation. Simultaneous detection of feature-specific encoding activities across multiple brain regions within the visual cortex and the analysis of feedforward-feedback patterns between different levels of primary/higher-order cortices represent critical challenges in advancing research on visual prediction encoding. However, existing studies suffer from limitations such as low detection resolution and narrow detection scopes. This study introduced a wide-field high-resolution confocal three-dimensional imaging technique, enabling synchronized acquisition of calcium signals from individual neurons across the whole cortex. During the experiments, transgenic mice were presented with various types of visual stimuli including

stripes and images, with stimulus presentation sequences encompassing random, sequential, and expectation-violating patterns. The experimental results indicated that the collected high-throughput neurons exhibited high orientation selectivity index (OSI), with primary and higher-level cortices displaying distinct temporal and spatial frequency encoding characteristics. Through high-resolution wide-field observation of neural activity, the transmission process of visual responses across the cortex was observed, indicating that the visual encoding process involved not only robust responses of individual neurons but also elicited collective neural encoding in surrounding brain regions. Furthermore, we observed that when stripe stimuli rotated according to clockwise or counterclockwise patterns, the visual cortex could anticipate the angle of the next appearing stripe, with both primary and higher-order visual cortices showing heightened responses to unexpected stripe stimuli. Additionally, compared to the primary visual cortex, higher-order cortical regions exhibited greater attention to unexpected stimuli. These findings further underscored the critical role of higher visual cortex in the visual prediction process, providing new insights for establishing visual prediction encoding models based on multilevel biological neural information.

Disclosures: **J. Xie:** None. **G. Xiao:** None. **J. Wu:** None. **Q. Dai:** None.

Poster

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Topic: D.06. Vision

Support: The publication was supported from was supported from ERDF-Project Brain dynamics, No. CZ.02.01.01/00/22_008/0004643.

Title: Unified spiking model of structured activity, traveling waves and optogenetic perturbation of the primary visual cortex.

Authors: T. RÓZSA, R. CAGNOL, ***J. ANTOLIK**;
Charles Univ., Prague, Czech Republic

Abstract: A fundamental operation of sensory systems is the integration of information across sensory space. In V1, spatial visual integration is mediated by lateral interactions across the cortical surface, primarily through horizontal axons in superficial layers, shaping cortical activity dynamics. Yet, the triad of visual information integration, underlying connectivity substrate, and cortical dynamics is not well understood. Lateral interactions in vision are typically studied using sensory stimulation through analysis of the lateral spread of information or interactions between multiple stimulated cortical sites. However, 'sensory-driven' methods conflate the complexities of feed-forward processing with recurrent interactions, making it difficult to disentangle individual contributions. An emerging alternative paradigm, not relying on sensory input, shows the cortex exhibiting complex, heterogeneous dynamics driven by mechanisms similar to those

in visually evoked activity, as evidenced by following three phenomena:
1. Spontaneous Structured Activity: Activity patterns that correlate with V1's functional maps, linking function to resting state dynamics.
2. Spontaneous Traveling Waves: Waves that propagate across the cortex consistent with speeds of unmyelinated lateral axons, show bias from the underlying functional organization, and influence behavior.
3. Optogenetic Perturbations: Optogenetic perturbations of ongoing activity can bridge the resting and visually evoked states.
The complexity and interconnectedness of these three phenomena requires an integrative approach. Computational models, ideally suited for this, allow for the exploration of interactions across these phenomena that are challenging to isolate experimentally. Yet computational models that cover all these phenomena are lacking. By using a computational model that includes spontaneous activity, traveling waves, and optogenetically evoked patterns, we aim to fill this gap. Our model not only accurately reflects a wide spectrum of experimental data but also generates testable predictions. This study unifies fragmented experimental findings, enhancing our understanding of these interlinked processes and paving the way for predictive, manipulable models of sensory processing in the brain.

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Poster

PSTR025: Sensorimotor Transformation: Behavior and Whole Animal

Location: MCP Hall A

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Program #/Poster #: PSTR025.01/F4

Topic: D.07. Visual Sensory-Motor Processing

Support: HHMI-HHWF fellowship

Title: Within-cell-type Synaptic Specificity underlying a Visuomotor Transformation

Authors: *M. DOMBROVSKI[1], Y. ZANG[2], H. JANG[3], C. R. VON REYN[4], G. M. CARD[2], S. L. ZIPURSKY[5];
[1]UCLA, Los Angeles, CA; [2]Neurosci., Columbia Univ., New York, NY; [3]Sch. of Biomed. Engineering, Sci. and Hlth. Systems, [4]BIOMED, Drexel Univ., Philadelphia, PA; [5]UCLA Chapter, Los Angeles, CA

Abstract: Visuomotor transformation (VMT), a vital process by which the brain converts vision into action, requires precise synaptic connectivity between sensory and motor neural circuits. Developmental and molecular origins of a VMT remain elusive. We address this gap by interrogating the visuomotor interface of *Drosophila* and leveraging single-cell transcriptomics, EM-connectomics, genetics and physiology to causally link genes and molecules with circuit function. Our earlier work identified a new fundamental wiring mechanism underlying a VMT (**synaptic gradients**), by which an object location in the eye coordinates transforms into

directional body movements. This transformation occurs between feature-detecting Visual Projection Neurons (VPN) and premotor Descending Neurons and is independent of axonal and dendritic topography. Individual neurons of the same VPN cell type become functionally heterogeneous depending on the region of the visual field they sample, thus displaying a continuous **within-cell-type synaptic specificity**. To unravel the molecular determinants of synaptic gradients, we performed a single-cell transcriptomic analysis of VPNs during development and found a remarkable degree of transcriptomic heterogeneity across single neuronal types, with most differentially expressed genes representing Cell Adhesion Molecules (CAMs) regulating synaptic specificity. Spatial gradients of gene expression matched the orientation of synaptic gradients, as inferred from approaches in genetics and spatial transcriptomics. We hypothesize that within-cell-type molecular gradients of DIP/Dpr and Beat/Side families of CAMs regulate axonal and dendritic synaptic gradients in the looming escape and motion detection circuits, respectively. These hypotheses have been validated through genetic perturbation analysis coupled with assays in behavior and physiology. Thus, we propose a model where gradients of CAMs determine within-cell-type synaptic specificity independent of the spatial organization of axons and dendrites.

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Poster

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.02/F5

Topic: D.07. Visual Sensory-Motor Processing

Title: Cell-type specific representation of temporal signals in behaving mice

Authors: Y. HUANG, L. COPELAND, T. STAMM, S. AMINNAJI, A. SHAMSNIA, H. PATIL, Y. ZHANG, *F. NAJAFI;
Georgia Inst. of Technol., Atlanta, GA

Abstract: Temporal expectation is the ability to anticipate the timing of future events based on prior experience, and is essential for learning, perception, and action in a dynamic environment. However, the neuronal mechanisms underlying temporal expectation signaling in the brain remain poorly understood. While previous studies have identified distributed temporal signals across brain regions, particularly in the cerebellum and visual-parietal cortical areas, the underlying cell-type specific circuits and interactions among these brain regions during temporal processing are yet to be determined.
We addressed this question in behaving mice by presenting a temporally regular sequence of auditory and visual stimuli, which included infrequent temporal violations. To investigate the cell-type specific mechanisms underlying temporal processing, we performed two-photon calcium imaging from Purkinje cells in the cerebellar cortex, as well as from excitatory and

inhibitory neuronal subtypes in the visual and posterior parietal cortex of awake, behaving mice. To identify the potential interactions among these brain regions during temporal processing, we manipulated one brain region while performing calcium imaging from the other regions. Our results suggest functionally diverse clusters of neurons in cerebellar and visual-parietal cortical regions, with distinct temporal coding properties. While some neurons are stimulus driven, some other neurons demonstrate temporal signaling.
Altogether, our findings begin to shed light on how cortical and cerebellar circuits process temporal expectation signals. Future experiments will investigate the cell-type specific computations that underlie temporal processing during active behavior.

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Poster

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Program #/Poster #: PSTR025.03/F6

Topic: D.07. Visual Sensory-Motor Processing

Support: The Connected Minds Program
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Title: A Comparative Analysis of Reach-to-Grasp Versus Reach-to-Place Movements

Authors: *N. PORDAVOODY[1], G. LUABEYA[2], X. YAN[2], V. BHARMAURIA[5], E. FREUD[3], P. J. KOHLER[4], J. CRAWFORD[3];
[1]Psychology, York university, Toronto, ON, Canada; [2]Ctr. for Vision Res., [3]Ctr. for Integrative and Applied Neurosci., [4]Dept. of Psychology, York Univ., Toronto, ON, Canada; [5]Neurosurg. and Brain Repair, Univ. of South Florida, Tampa, FL

Abstract: Many studies have examined the characteristics of reaching to grasp, but relatively few have studied the placement component. Grasping and placing share some similar features, such as the need to precisely localize and orient the hand but differ in cognitive intent of the task and both visual and somatosensory feedback. Our study is constituted of a within-subjects design, with each participant alternatively performing grasp and placing movements toward an elongated cube at one of two randomized locations (left / right of midline) and two orientations (clockwise / counterclockwise), with each of these 8 conditions repeated 20 times for a total of 160 trials. The task begins with the subject fixating their eyes on a central fixation point and placing their hand on a frontal home position. The object is placed on a rectangular template resting at one of the four locations/orientations on a tilted surface in front of the home position. An LED light illuminates the object for a variable duration (1000-1500ms), then Fixation light and illumination turn off acting as a Go signal. The participant reaches for the object, and returns it to the home position, with free gaze. In the second half of the task, the template position is

randomized, illuminated again, and the participant has to place the object on the placement holder with the same time sequence as the grasp, thus randomizing and equalizing the grasp and placement tasks as much as possible. A preliminary analysis of 7 participants suggests several general trends: peak velocity of counterclockwise movements (for both Grasping & Placing tasks) was higher than that of clockwise movements, peak velocity of Grasping and Placing movements with object position on the right was higher than that on left, and duration showed a significant 2-way interaction between Orientation and Task. Additional participants are required to attain sufficient power for conclusions and a more detailed analysis will be done on the three-dimensional components of both hand location and orientation.

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Poster

PSTR025: Sensorimotor Transformation: Behavior and Whole Animal

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Program #/Poster #: PSTR025.04/F7

Topic: D.07. Visual Sensory-Motor Processing

Support: R01 NS130917

Title: Fear-induced, visually-guided collision avoidance escape behavior in mice

Authors: M. SEVERSON[1], M. VALLENS[2,4], A. HO[3], I.-C. TAN[2], V. AKHANOV[3], R. B. DEWELL[2], N. LI[2,5], M. A. SAMUEL[3], ***F. GABBIANI**[2];
[1]Neurosci., Brandeis Univ., Waltham, MA; [2]Neurosci., [3]Huffington Ctr. On Aging, Baylor Col. of Med., Houston, TX; [4]John Hopkins Univ., Baltimore, MD; [5]Neurobio., Duke Univ., Durham, NC

Abstract: Approaching stimuli, such as those emulating an oncoming predator on a direct collision course, elicit an escape response critical for survival in many animal species. The biophysical mechanisms underlying such visually guided escape behaviors have been previously characterized in a variety of animals, such as locusts, pigeons, vinegar flies, fish, and amphibians. Here, we provide evidence that mice display similar collision detection escape behavior in response to looming stimuli. Using a fear conditioning paradigm, we trained mice to associate an aversive foot shock with a looming stimulus as they traversed a rectangular maze to access a water reward delivered on an elevated platform at the site of stimulus presentation. The mice learned to anticipate the shock delivered at the time of the looming stimulus' projected collision by initiating an escape behavior away from the platform. By varying the looming stimulus size to speed ratio, we established that the escape behavior from looming stimuli follows an angular size threshold model, whereby the escape is initiated at a fixed delay after the stimulus reaches a fixed angular size on the retina. Interfering with vision through surgical or pharmacological ablation of retinal ganglion cells significantly affects the probability of escape.

These behavioral experiments indicate that we can effectively train mice to reliably escape from a looming stimulus which imitates a natural predator through a fear conditioning paradigm. In addition, this escape behavior is vision-dependent, likely through a defined subset of retinal ganglion cells.

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Poster

PSTR025: Sensorimotor Transformation: Behavior and Whole Animal

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Topic: D.07. Visual Sensory-Motor Processing

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Title: Goldfish horizontal, vertical, and torsional OKR adaptations reflect distinctive head motion experience

Authors: *S. TADOKORO[1,2,3], S. MIKI[1], T. UENO[4], T. YAMANAKA[4], T. HIRATA[5], Y. HIRATA[4,6,7,8];
[1]Chubu Univ., Kasugai, Japan; [2]Otolaryngology, Head and Neck Surgery, National Defense medical college, Tokorozawa, Japan; [3]Japan Air Self-Defense Force, Ichigaya, Japan; [4]Robotic Sci. and Technol., Chubu Univ., Kasugai, Japan; [5]Cognitive and Psychological Sci., Nagoya Univ., Aichi, Japan; [6]Academy of Emerging Science, Chubu university, Kasugai, Japan; [7]AI and Robotics, Chubu university, Kasugai, Japan; [8]Center for Mathematical Science and AI, Chubu university, Kasugai, Japan

Abstract: Optokinetic response (OKR) and vestibulo-ocular reflex (VOR) stabilize retinal images during locomotion. As other biological functions, these reflexive eye movements may be optimized for an animal's motion patterns in its habitat. Given the unique swimming behavior of fish, their distinctive three-dimensional (3D) motion patterns might be reflected in the 3D horizontal (H), vertical (V), and torsional (T) OKR and VOR characteristics. In this study, we employed goldfish and evaluated H (n=9), V (n=9) and TOKR (n=10) and their adaptations. We used a bidirectional velocity square wave visual stimulus (0.05Hz, ±20deg/s) for 90 min, followed by 60-min in darkness to assess memory retention. Additionally, we measured head angular velocity of a freely-swimming carp by using a 3D gyro-sensor (LP-RESEARCH Inc., LPMS-B2) fixated on its head, and also evaluated head motion of a freely-swimming goldfish during predation. Results showed that naïve animals presented minimal V and TOKR in contrast to their robustly induced HOKR. However, V and TOKR gradually manifested during the 90-

min visual training, reaching to gains (eye velocity / visual stimulus velocity) greater than 0.25. Interestingly, while VOKR gain increased in both upward and downward directions, TOKR gain increased only for extorsion. The memory retention of H and VOKR rapidly decayed in darkness after 5 min and remained at a similar level thereafter. By contrast, extorsional OKR memory decayed much slower, suggesting that extorsional OKR memory may be formed through mechanisms different from H and VOKR adaptation. Amplitude spectrum of HOKR in naïve animals indicated low-pass characteristics in the evaluated frequency range (0.05~0.5Hz), which increased during the visual training, keeping the low-pass characteristics. By contrast, V and TOKR indicated rather flat amplitude spectra in naïve animals, whose values at lower frequencies increased slightly more after the training. The amplitude distribution of the freely-swimming carp head angular velocity around the yaw axis exhibited significantly greater variance than those around the pitch and roll axes, corresponding to robust HOKR gain and significantly lower V and TOKR gains in naïve fish. The freely-swimming goldfish during predation displayed asymmetrical head motion in pitch as observed in TOKR, with larger and faster pitch-down motion, which requires extorsion to stabilize vision, compared to pitch-up motion. These qualitative consistency between 3D OKR and the corresponding 3D head motion suggests that their natural 3D head motion might be reflected in the characteristics of 3D OKR and their adaptabilities.

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Poster

PSTR025: Sensorimotor Transformation: Behavior and Whole Animal

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.06/F9

Topic: D.07. Visual Sensory-Motor Processing

Title: Coordinated responses of microsaccade and pupil in salience detection

Authors: *Y. ZHAO[1], E. RILEY[2], A. K. ANDERSON[3], E. D. DE ROSA[2];
[1]Dept. of Psychology, [2]Cornell Univ., Ithaca, NY; [3]Dept. of Psychology, Cornell Univ., Syracuse, NY

Abstract: Microsaccades and pupil size changes, regulated by higher-level cognitive processes such as salience detection, exhibit interactions that are not fully understood. The neural pathways for salience encoding, microsaccade generation, and pupil psychosensory responses are connected at the superior colliculi (SC), suggesting potential coordinated responses. We utilized an oddball test with a pseudorandom presentation of salient targets (large pink circles, frequency=20%), non-salient controls (small pink circles, frequency=60%), and alter-luminant stimuli (small white circles, frequency=20%) on 48 participants (31 female, 17 male) using an Eyelink 1000+ eye-tracker to collect pupil diameters and gaze position. Participants were separated into age groups of young (18-44, n=19), middle-aged (45-64, n=12), and old (65 or

more, n=17). Microsaccades were detected with the Engbert and Kliegl Algorithm (2003). In study one, we examined whether there are coordinated responses of microsaccades and pupils to saliency and luminance changes across life span using mixed-effects linear models and two-way mixed-effects ANOVA. Significant condition effects were found for pupil responses in maximum size change, area under the curve, and rate of change, but not in latency to maximum change. For microsaccades, significant condition effects were observed in amplitude and onset frequency, but not in peak velocity, indicating that saliency significantly influenced orienting responses of both microsaccades and pupil, while luminance changes induced only an autonomic reflex in pupils. In study two, we explored how pre-stimuli onset microsaccades might affect subsequent pupillary responses in orienting. The same analysis methods were used as in study one, and the analysis revealed that pre-trial microsaccades significantly impacted the latency to maximum pupil size change, with a notable suppression of pupil dilation in control and alter-luminant conditions compared to salient conditions. Overall, age was a significant influencer of condition effects in both studies. We conclude that there is a coupling between orienting microsaccadic and pupillary responses. Besides, we infer that microsaccades might suppress a brain structure upstream of the SC in the sympathetic pathway, thus influencing pupil dilations in control and alter-luminance conditions while maintaining the orienting dilation response in salient conditions.

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Poster

PSTR025: Sensorimotor Transformation: Behavior and Whole Animal

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Program #/Poster #: PSTR025.07/F10

Topic: D.07. Visual Sensory-Motor Processing

Support: Stanford HAI / Wu Tsai Neuro Grant
Stanford Norman H. Anderson Fund

Title: Overconfidence in motor command prediction during visuomotor tracking

Authors: *J. RYU, J. L. GARDNER;
Psychology, Stanford Univ., Stanford, CA

Abstract: Precise and speedy control of an object in the external world, be it a tennis racket, a virtual character, or a computer cursor, requires combining predictions based on intended movement with sensory feedback. For example, when tracking a moving target with a pointer (Mulligan et al., 2013; Bonnen et al., 2015), an ideal actor should make a prediction for where the pointer will be based on their motor command and combine that with visual sensory feedback to achieve optimal control. Here, we ask whether human subjects performing such a tracking task use such an optimal strategy. During tracking, we modulated the position of the target and the pointer each with temporally autocorrelated noise, and observed the subjects' sensitivity to these

modulations as they were actively moving the pointer. An ideal actor should not distinguish between motion added to the target or the pointer: either should guide their motor movements equally well. Instead, we found that subjects (n=9) were less sensitive to motion on the pointer than on the target. Specifically, we computed the cross-covariance of the human tracking responses with the independent, uncorrelated portion of the modulation signals injected into either the pointer or the target. We found that subjects displayed delayed and longer responses to the pointer modulations compared to those to the target modulations. To determine whether this difference was due to differences in the actual motion statistics of the target and pointer, we perturbed the target position with the same sequence of pointer velocities used in the main experiment. We found that the difference in motion sensitivity could not be fully accounted for by differences in motion statistics, as the cross-covariance was less delayed and shorter than when motion was added to the pointer. Simulations show that the human responses to the pointer modulations were consistent with a Linear-Quadratic-Gaussian actor (Ryu and Gardner, 2022; Straub and Rothkopf, 2022) with a smaller Kalman gain of the pointer position than that of the target. The smaller Kalman gain required to model the performance of the subjects suggests that subjects were discounting sensory evidence from the pointer and weighting more heavily their prediction of where the pointer would be based on their motor command. Overall, the results are consistent with an actor with attenuated sensory processing (Blakemore et al., 2000; Bays and Wolpert, 2007) of visual stimuli under active control or an actor overconfident about the visual consequences of their actions.

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Poster

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Program #/Poster #: PSTR025.08/F11

Topic: D.07. Visual Sensory-Motor Processing

Title: Experimentally testable Data driven Geometric models of sensorimotor integration on low dimensional manifolds

Authors: J. PARK[1], A. CAMASSA[2], M. B. AHRENS[3], T. J. SEJNOWSKI[4], ***G. M. PAO**[5]; [1]Biol. Nonlinear Dynamics Data Sci. Unit, Okinawa Inst. of Sci. and Technol. Grad. Univ., Onna, Okinawa, Japan; [2]Salk Inst. for Biol. Studies, Cardiff by the sea, CA; [3]Janelia Res. Campus / HHMI, Ashburn, VA; [4]Salk Inst., La Jolla, CA; [5]Okinawa Inst. of Sci. and Technol., Kunigami district, Okinawa, Japan

Abstract: In the last decade or so neuroscience has gone from predominantly single neuron recordings to large scale recordings of up to a million neurons. This transformation in data collection allows us to question more broadly what is the nature of the population code of large numbers of neurons and how do these relate to behavior. Linear methods have shown poor predictive power. Common dimensionality reduction approaches fail to provide an

understandable representation of the population code. Of these, principal component analysis (PCA) is probably the most common method. However these dimensionality reduction methods produce latent variables that are experimentally not testable as the latent components do not have a direct correspondence to neither brain areas nor neurons . Here in the following work, we develop a novel dimensionality reduction algorithm that uses a dynamical systems theory framework, the Takens theorem, and its application for causal inference, the convergent crossmapping (CCM) algorithm, to produce a predictive data driven geometric model based on low dimensional manifolds that generically maps brain activity to behavior without latent variables. Here every variable corresponds to either a single or a population of identifiable neurons or brain area. The dimensionally reduced representation is a manifold mapping that can predict future behaviors of the animal based on neural activity and is sensitive to sensory input where each orthogonal axis in the ambient space of the manifold corresponds to an observable neuron, population of neurons or brain area. As such it allows for experimental verification as it produces falsifiable predictions of the contribution of candidate brain components that contribute to behavior. We name this method Causal Compression. Causal compression can be used as a single manifold or as a network of manifolds that can simulate an entire brain at single neuron resolution. In the following example we show that using recordings of whole brain zebrafish with over 10^5 neuron, one can map sensory input to brain activity and ultimately to motor output using a manifold of surprisingly low dimensionality to predict future behaviors of drosophila and larval zebrafish.

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Poster

PSTR025: Sensorimotor Transformation: Behavior and Whole Animal

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Topic: D.07. Visual Sensory-Motor Processing

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Title: Cell-type specific representations in the dorsomedial striatum emerge during learning and support the selection of visually guided actions

Authors: *G. RODRÍGUEZ-MORALES[1], B. GRAHAM[2], M. HOWE[3];
[1]Boston Univ., Boston, MA; [2]Boston Univ. Undergraduate Program In Neurosci., Boston, MA; [3]Boston Univ., Needham, MA

Abstract: The ability to select appropriate actions based on environmental cues is critical to the survival of all species. The striatum, the main input nucleus of the basal ganglia, has been proposed to participate in this process by integrating converging inputs from sensory, motor, and

cognitive cortices and influencing action via basal ganglia output nuclei. However, evidence for the striatum's role in sensory guided action selection is limited and conflicting, and it is unknown how activity in populations of striatum output neurons supports learning and execution of cued actions. We performed simultaneous 2-photon calcium imaging of identified direct and indirect pathway spiny projection neurons of the dorsomedial striatum (dSPNs and iSPNs respectively) while head-fixed mice learned and performed an associative, visually guided two-choice task. During stable performance, sub-populations of dSPNs and iSPNs were activated to the presentation of visual cues and to the onsets of directional actions. The population activity of both sets of SPNs, those active at the onset of cues and actions, successfully predicted directionality of subsequent behavior in the task. However, unlike the population responses at the onset of actions, the relative level of activation of dSPN and iSPN population responses at cue onset were imbalanced, with larger activity levels for dSPNs than iSPNs. During initial learning, this imbalanced activation of dSPNs and iSPNs at the onset of cues was not present, nor was the ability to predict subsequent behavior directionality. There were no detectable differences in action onset representations between stable behavior and initial learning. Collectively, these results suggest that the learning of visually guided actions involves a gradual reshaping of cue representations leading to the emergence of action-related information and imbalanced dSPN/iSPN activation prior to the execution of the movement. To test whether the activity we measured contributes directly to correct task execution, we optogenetically silenced the dorsomedial striatum on subsets of trials during stable performance and found immediate impairments in choice behaviors, specific to the inhibited trials. This effect was not due to non-specific effects of the light or gross impairments in locomotion. Overall, these results suggest a mechanistic explanation for how associative learning can shape cell-type specific striatal ensembles to support real-time cue guided action selection.

Disclosures: G. Rodríguez-Morales: None. **B. Graham:** None. **M. Howe:** None.

Poster

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Support: BridgesDH NRT Fellowship, NSF Award # 2125872
West Virginia University Center for Foundational Neuroscience Research and Education
NIH Award Number 1 R03 HD099426-01A1

Title: Human interlimb speed perception during locomotion peaks in young adulthood and declines with age

Authors: *E. HERRICK[1], C. BRANDMEIR[2], S. YAKOVENKO[2,1,3,4];
[1]Chem. and Biomed. Engin., [2]Human Performance, [3]Neurosci., [4]Rockefeller Neurosci. Inst., West Virginia Univ., Morgantown, WV

Abstract: Sensorimotor interactions are essential for navigating in a complex environment. Yet, the principles of control underlying limb movements and their modifications throughout the lifespan are hindered by the high-dimensional complexity of both motor and sensory pathways. The nervous system solves this problem with the help of a hierarchical organization that embeds neuromechanical dynamics at spinal and supraspinal levels. Recent computational work indicates that the limb speed signal is expressed within the control pathways, offering the opportunity to test the consequent predictions within the sensory pathways of the sensorimotor loop. We expect that the kinesthesia of limb speed is progressively fine-tuned during the development period and deteriorates during the aging period as the neural and musculoskeletal systems undergo growth, reorganization, and deterioration processes. Using a psychometric testing approach, we examined lower-limb velocity perception in four age groups: children (aged 6-12), young adults (aged 18-34), middle-aged adults (aged 35-59), and older adults (aged 60+). Each participant was asked to walk on a split-belt treadmill and identify which leg was moving faster during a schedule of interlimb speed differences from 1% to 30%. In this two-alternative forced-choice task, the performance was quantified with the just noticeable difference at 75% probability of detection (JND75). We found that the young adult group had a significantly lower JND75 than the child, middle-aged, and older adult groups. Our results indicate that limb control improves from childhood, peaking in young adulthood, and decreases as we age. With this insight, we can inform training protocols to optimize the development of coordination in children and rehabilitate walking abilities in older adults.

Disclosures: E. Herrick: None. **C. Brandmeir:** None. **S. Yakovenko:** None.

Poster

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Topic: D.07. Visual Sensory-Motor Processing

Support: GVA CIDEGENT 2021-028 (SPAIN)

Title: A collicular circuit for routing visual distractions into goal-dependent behavior

Authors: K. SONG[1], G. USSEGLIO[2], D. MARIATOS METAXAS[3], S. MOROU[4], K. MELETIS[5], A. KUMAR[6], I. LAZARIDIS[7], ***A. A. KARDAMAKIS**[8];
[1]Inst. de neurociencias, San Juan de Alicante, Spain; [2]Inst. de Neurociencias, Inst. de Neurociencias, Alicante, Alicante, Spain; [3]Med. Univ. of Vienna, Vienna, Austria; [4]Neurosci. Inst., Sant Joan d' Alacant, Spain; [5]Karolinska Inst., Stockholm, Sweden; [6]KTH Royal Inst. of

Technol., Stockholm, Sweden; [7]MIT, MIT, CAMBRIDGE, MA; [8]Neurosci. Inst., Alicante, Spain

Abstract: Can we predict when a visual distractor will capture our attention? Visual distractors can trigger overt responses or remain unattended. The circuitry underlying this action selection remains poorly understood due to the predominant use of paradigms restricted to head-restrained animals in multisensory tasks, while relevant visual behaviors in mice are centered around fear or escape responses. Here, we demonstrate a novel paradigm using self-initiated visual search to trigger animal navigation, enabling the randomized mid-flight presentation of salient visual stimuli to assess distractibility within the context of goal-dependent behavior. Computer vision methods were applied on imaging data to capture behavioral state transitions, which ranged from attentive distractor engagement to trajectory perturbations or stimulus neglect. We computed several behavioral variables from the animals' movement patterns to characterize these states, including an initiation density function to predict the probability of visual distraction level based on prior trials of search behavior. During this attention-distractor paradigm, we manipulated and recorded from glutamatergic (vGluT2), including medullar projection-specific cells, and GABAergic (vGAT) neurons in the intermediate layer of the lateral superior colliculus (l.SCi) to study whether this conserved circuitry is capable of tuning visual distractors in and out from behavior. *In vivo* cell-type-specific calcium recordings -via fiber photometry- reveal their involvement to this behavior, while their optogenetic and chemogenetic manipulation (activation and/or inhibition) enables direct control of visual distractor resilience allowing for the selective increase or decrease. We propose that local l.SCi inhibition can set a visual distractor alert-to-suppress threshold during task-dependent behavior.

Disclosures: K. Song: None. **G. Usseglio:** None. **D. Mariatos metaxas:** None. **S. Morou:** None. **K. Meletis:** None. **A. Kumar:** None. **I. Lazaridis:** None. **A.A. Kardamakis:** None.

Poster

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Topic: D.07. Visual Sensory-Motor Processing

Support: Howard Hughes Medical Institute Freeman Hrabowski Fellowship
E Matilda Ziegler Foundation for the Blind Grant

Title: A comparative quantification of locomotion behavior in rats and tree shrews

Authors: *M. E. CASSITY[1], E. KEMPKES[1], K. ALBERTINI[2], M. SEDIGH-SARVESTANI[1]; [1]Neurobio. and Behavior, Cornell Univ., Ithaca, NY; [2]Max Planck Florida Inst. for Neurosci., Riviera Beach, FL

Abstract: Technological advances have enabled the study of neural circuits in freely moving animals. Free moving paradigms are especially important for sensory processing studies because

body movements shape the statistics of sensory inputs. However, freeing the animal brings new challenges. Specifically, an estimate of the animal's body movements must be measured and distilled into a meaningful representation. Such datasets can help to characterize species-specific sensorimotor input patterns during free moving behavior, which will be critical to understanding neural activity recorded under natural conditions.

Here we characterize and compare movement behavior in freely moving rats and tree shrews. Rats are nocturnal, not highly visual, and have a relatively limited range of movements including climbing, rearing, and short jumps. Tree shrews are diurnal, highly visual, and have a rich motor repertoire which includes climbing, rearing, and short jumps, as well as long jumps, flips and other acrobatic maneuvers. We chose these species because they are similarly sized but have distinct locomotion behaviors.

We recorded behavior in freely moving animals in the same large home-cage, using video cameras with high spatiotemporal resolution. We quantified body position across time using published methods to extract 'pose' from behavior videos. We extracted further information from this pose data by considering the relationship across space and time between different body parts. This allowed us to produce a low-dimensional visualization of behavior, as characterized by separable clusters containing spatiotemporal patterns of body movements. To explore this low-dimensional behavior space, aka latent space, we developed a graphical user interface including an interactive plot mapping the behavior clusters to their corresponding images in the behavior videos. This enabled us to determine whether clusters in the latent space contained meaningful sub-behaviors. Using these tools, we confirmed that clusters in the latent space were related to specific types of movement, such as rearing, in rats and tree shrews. We also found a subset of shared and distinct clusters in the behavioral latent space of rats vs. tree shrews. We believe such characterization is critical for untangling neural activity recorded in the brain of different laboratory animals using increasingly popular natural paradigms. Our results serve as a foundation for future work focused on multi-model classification of behavior based on both movements and the resulting movement-generated sensory inputs.

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Poster

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Topic: D.07. Visual Sensory-Motor Processing

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Title: A circuit for evasive flight maneuvers in Drosophila centered around the descending neuron DNp03

Authors: *H. CROKE[1], H. JANG[1], T. STURNER[2], M. COSTA[3], K. EICHLER[3], J. AUSBORN[4], C. R. VON REYN[1,4];
[1]Sch. of Biomed. Engineering, Sci. and Hlth. Systems, Drexel Univ., Philadelphia, PA; [2]Neurobio. Devision, Neurobio. Division, MRC Lab. of Mol. Biology, Cambridge, UK, Cambridge, United Kingdom; [3]Univ. of Cambridge, Cambridge, United Kingdom; [4]Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Sensorimotor transformations are necessary across species, yet we rarely have the capability to dissect the circuits involved in these computations. With recent advancements in electron microscopy, we now have the full *Drosophila* central brain and ventral nerve cord (VNC), analogous to the vertebrate spinal cord, allowing us to map the circuits involved in complex sensory to motor behaviors at the level of individual synapses. Here, we focus on a sensorimotor circuit surrounding the descending neuron, DNp03. DNp03 is predicted to receive ipsilateral visual input and alter contralateral wing behavior, but the type of information it integrates and the behavior it coordinates is unknown. We identified major pre- and postsynaptic partners to DNp03 in three available electron microscopy datasets - the full adult fly brain (FAFB) dataset, the hemibrain connectome, and the female adult ventral nerve cord (FANC) dataset. We found visual projection neurons including Lobula Plate Lobula Columnar Type 1 (LPLC1), Lobula Columnar Type 4 (LC4), and Lobula Plate Lobula Columnar Type 4 (LPC4) are major population inputs to DNp03. Both LPLC1 and LC4 respond to looming stimuli, or the 2D projection of an approaching object on a direct collision course. To evaluate if DNp03 is looming responsive, we used whole-cell electrophysiology to record from DNp03 and found it robustly responds to ipsilateral, but not contralateral loom across various size to speed ratios. Looming stimuli, depending on specific visual and behavior state parameters, can evoke different behavioral outputs. For example, flies can respond to looming stimuli by taking off, landing, or performing evasive flight saccades. We therefore investigated downstream synaptic partners in the VNC to gain predictions about behavioral output. We found that DNp03 synapses onto the dorsal longitudinal motor neurons, which power the downstroke, and contralateral wing steering motor neurons, which are active during saccades. Through unilateral optogenetic activation, we found that DNp03 activation elicits contralateral saccades. Upon silencing of DNp03, flies showed a significant reduction of saccade behaviors when presented with looming stimuli. All together, through a combination of connectomics, electrophysiology, optogenetics, and silencing experiments, we find that DNp03 integrates ipsilateral looming stimuli to evoke a contralateral saccade, steering away from a perceived threat. DNp03's circuit is one of few that directly maps connectivity to behavior, allowing future investigations of sensorimotor transformations through perturbations of individual components.

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Poster

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NIGMS T32 GM142494

Title: Thalamic control of a visual critical period and motor behavior

Authors: *J. HAGETER[1], J. STARKEY[1], E. HORSTICK[1,2];
[1]West Virginia Univ., Morgantown, WV; [2]Department of Neuroscience, West Virginia University School of Medicine, Morgantown, WV

Abstract: Environmental influence shapes the brain during early development. Critical periods (CP) are discreet developmental windows where the environment has a profound impact on structural and functional changes to a circuit. CPs are responsible for the development of an array of sensory systems such as vision, hearing, and touch. There is a deep understanding of how CPs present in higher order brain structures such as cortical regions, however, little is understood about how sub-cortical regions act to shape the brain during CPs. This work investigated the mechanisms in which the thalamus, a central brain region responsible for relaying sensory information to other brain regions, acts to shape circuit structure and function during a CP. To answer this, we took advantage of a robust zebrafish search strategy following the loss of light where zebrafish will engage in a preferentially biased swimming pattern in tightly coiled circles to find a source of illumination, either in a leftward or rightward direction. This motor bias and bias identity is maintained by a subset of inhibitory thalamic neurons coined the asymmetry maintaining neurons (AMNs). To understand how this motor bias forms, we developed an assay to control visual experience during early development by embedding zebrafish larvae in low melting point agarose (LMP). During LMP embedding, larvae are provided visual experience to either one or both eyes. We found that providing unilateral visual experience during this developmental window, we could induce bias to develop contralaterally to the experienced eye. This induction is only possible during the critical window from 2 to 4 days post fertilization. Using functional imaging of the thalamus and AMNs we show that distinct regions encode visual experience and display matching functional asymmetry with turn bias performance. This functional asymmetry was not present in other visual processing areas. Through targeted multiphoton ablation, we determined that these thalamic regions functionally dictate the identity of motor bias. We also show that the AMNs are inhibitory neurons expressing the gamma-aminobutyric acid (GABA) synthetic enzyme, glutamate decarboxylase (gad1b/ gad2). We also determined that the timing of this CP is controlled by inhibitory signaling. This work has developed a new model to investigate mechanisms underlying the sub-cortical mechanisms of CP plasticity. Here we provide a neuron level role for CP plasticity in the thalamus and how it leads to functional, and behavioral changes.

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Poster

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Program #/Poster #: PSTR025.15/F18

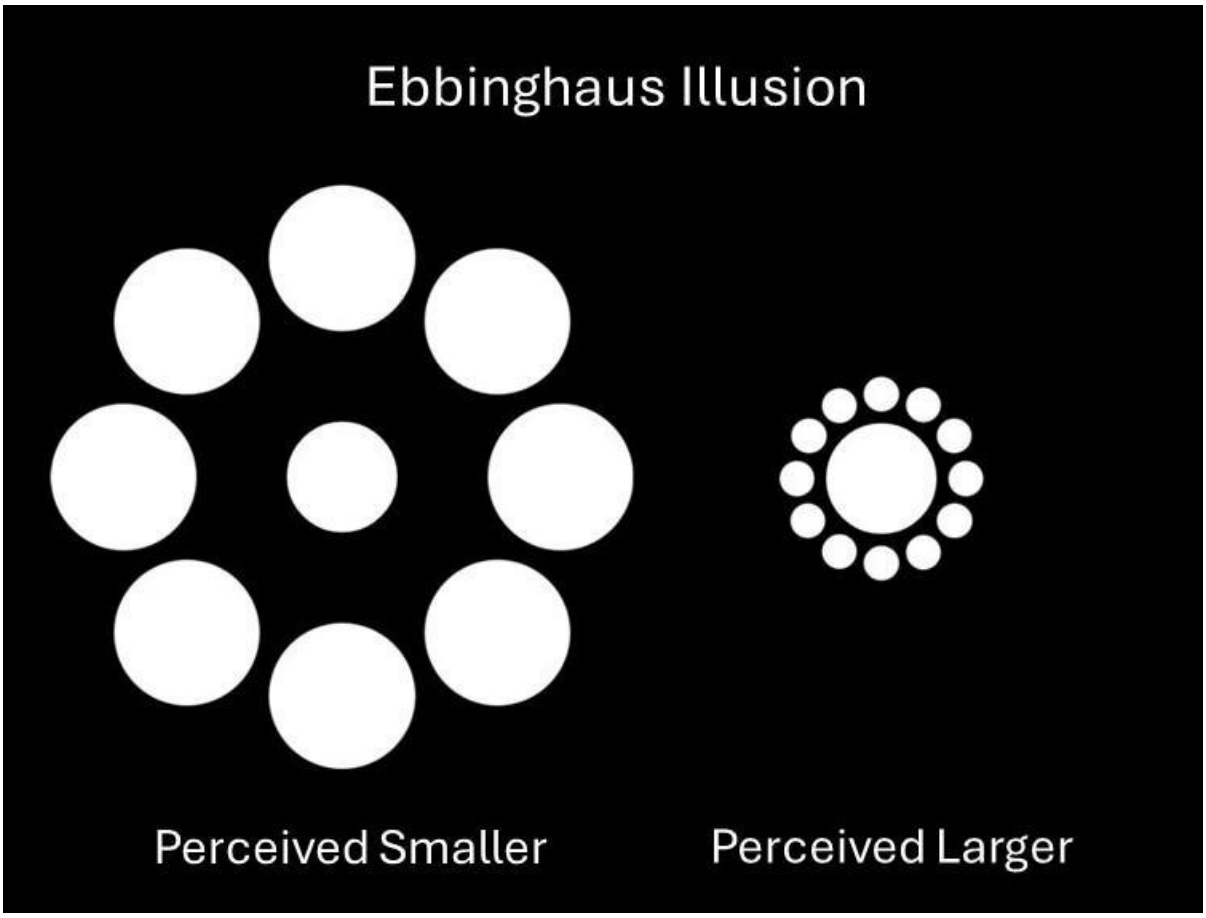
Topic: D.07. Visual Sensory-Motor Processing

Support: NSERC Discovery Grant

Title: Are onscreen cursor movements susceptible to visual illusions? Exploring perception-action interactions in a virtual environment

Authors: *R. W. LANGRIDGE, J. J. MAROTTA;
Dept Psychology, Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: The two-visual systems hypothesis of vision (TVSH) proposes a functional distinction between a 'perception' system, responsible for our conscious perception of a stimulus, and an 'action' system, responsible for mediating our visually guided actions toward that stimulus (Goodale & Milner, 1992). Supporting evidence for the TVSH has demonstrated that perceptions of a stimulus are susceptible to size-contrast illusions such as the Ebbinghaus, or "Titchener Circles" illusion, whereas visually guided actions (e.g., grasping) toward that stimulus are tuned to its veridical size. An interesting variation on the classic study of perception-action interaction is to explore how actions toward virtual stimuli are influenced by the perceptual features of the virtual environment in which they occur (e.g., using a laptop trackpad to control an onscreen cursor). The current confirmatory study tested for the presence of a perceptual influence on participants' visually guided cursor movements toward Ebbinghaus stimuli. Participants used a trackpad to click on targets perceived as either larger or smaller than their true size. Click-point accuracy was measured to test for an effect of the illusion on performance. In Experiment 1, participants were provided full vision of the target. Participants were significantly more accurate when clicking the Perceived Larger target compared to the Perceived Smaller target, suggesting participants' perception of target size influenced their performance. In Experiment 2, the target disappeared at the onset of the trial, and participants had to rely on their memory of the target to perform the task. There was no difference in click-point accuracy between the illusory targets when participants performed the task without visual feedback. Conclusion: Onscreen cursor movements are susceptible to perceptual influence, but only in conditions when the onscreen targets are visible. These results contribute to the TVSH by further elucidating the circumstances in which visually guided behaviour is influenced by perceptual processing.



Disclosures: **R.W. Langridge:** None. **J.J. Marotta:** None.

Poster

PSTR025: Sensorimotor Transformation: Behavior and Whole Animal

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Topic: D.07. Visual Sensory-Motor Processing

Support: Human Frontiers LT0019

Title: Neural circuits for maintaining heading using visual feedback

Authors: *G. ATLAN, G. BOUVIER, M. SCANZIANI;
Dept. of Physiol., UCSF, San Francisco, CA

Abstract: Motor functions in sighted animals rely on visual feedback. During locomotion, full-field shifts of the visual environment trigger corrective movements to maintain straight forward heading. This reflexive behavior is crucial for the ability to locomote, and as such it is conserved

throughout evolution, from invertebrates to humans. However, this behavior has been difficult to study in mammals, and its underlying neural circuitry is poorly understood. We developed an assay to reliably evoke corrective turns in freely-locomoting mice via closed-loop manipulation of visual feedback, enabling the study of the mammalian neural circuitry for maintaining heading. We find that corrective turns are triggered by the eye experiencing a temporo-nasal shift of the visual environment. Furthermore, we find that mice rely on visual cortex during this behavior. This ongoing work sets the stage for addressing a wide range of fundamental questions regarding the anatomical circuitry and the physiological mechanism underlying an essential sensorimotor transformation for maintaining heading in mammals.

Disclosures: G. Atlan: None. **G. Bouvier:** None. **M. Scanziani:** None.

Poster

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Topic: D.07. Visual Sensory-Motor Processing

Support: HHMI Principal Investigator (Scanziani)
Jane Coffins Child - HHMI Fellow (Purandare)

Title: The vestibular nucleus in mice encodes active head movements

Authors: *C. PURANDARE[1], G. BOUVIER[2,3], M. SCANZIANI[4];
[1]Physiol., Univ. of California San Francisco, San Francisco, CA; [2]Physiol., Univ. of California, San Francsico, San Francisco, CA; [3]Neurosci., CNRS Univ. Paris-Saclay Campus CEA, Saclay Paris, France; [4]Univ. of California, San Francisco, San Francisco, CA

Abstract: The vestibular nucleus in mammals is a brainstem structure which receives input from the vestibular canals and the otolithic organs and is thus posited to broadcast information about head movements to the rest of the brain. Most of our understanding about the activity of the vestibular nucleus comes from single cell recordings in experimentally controlled head movements. How vestibular nucleus neurons report head movements in unconstrained, freely moving animals remains largely unexplored. We thus performed extracellular recordings from the vestibular nucleus with linear probes chronically implanted in unrestrained mice whose head movements were monitored with inertial measurements units affixed to the head and with a top view camera. The recording sites were confirmed histologically *post hoc*. We focused our analysis on the response of vestibular neurons to head velocity in the clockwise (CW) and counterclockwise (CCW) direction along the azimuth. The vast majority (~70%) of vestibular nucleus neurons were modulated by head movements. The largest fraction responded similarly to movements of the head in either direction along the first principal component (e.g. clockwise and counterclockwise along the azimuth) and in most of these neurons, the firing rates increased with head velocity (Fig A). In a smaller fraction of neurons, the firing rates increased with increasing

head velocities in one direction and decreased with increasing head velocities in the opposite direction (Fig. B). Further, we found that head velocity encoding was widespread in the rodent brain, spanning the brainstem, cerebellum, midbrain as well as cortex. Our work suggests that the vestibular nucleus neurons can encode speed and direction of actively performed head movements thereby furthering our understanding of the sensory encoding in the rodent brainstem.

Disclosures: C. Purandare: None. **G. Bouvier:** None. **M. Scanziani:** None.

Poster

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Topic: D.07. Visual Sensory-Motor Processing

Support: NIH Grant K99EY033850
HHMI

Title: The Cognitive Consequences of Motor Commands During REM Sleep Reveal an Internal Model of the World

Authors: *Y. SENZAI[1,2,3], M. SCANZIANI[4,5];
[1]Univ. of California, San Francisco, San Francisco, CA; [2]Howard Hughes Medical Institute, San Francisco, CA; [3]Department of Neuroscience, Northwestern University, Chicago, IL; [4]Dept. of Physiol., Univ. of California, San Francisco, San Francisco, CA; [5]Howard Hughes Medical Instiute, San Francisco, CA

Abstract: Vivid dreams mostly occur during a phase of sleep called REM. During REM sleep the brain's representation of heading keeps shifting like that of awake animals moving through their environment. What causes these shifts, given the immobility of the sleeping animal? We hypothesized that motor commands generated in the sleeping brain, despite not being executed, shift the representation of heading as if they were executed. We tested this hypothesis in mice, by recording from the superior colliculus, a midbrain structure whose activity triggers head turns in awake animals, in order to decode motor commands, and from the anterior thalamus, a structure whose activity represents heading. We have discovered that, during REM sleep, activity in the superior colliculus resembles that in awake animals. Furthermore, this activity predicts shifts in the representation of heading, as if the head had turned. Finally, we have discovered that following unilateral silencing of the superior colliculus the representation of heading keeps turning in the same direction, ipsilateral to the silenced colliculus.These observations indicate that the superior colliculus, perhaps by orchestrating sensorimotor circuits in the sleeping brain, can update the internal representation of heading during REM sleep. Thus, during REM sleep, the brain uses its internal model of the world to represent the consequences of an animal's action even when said action is not executed.

Disclosures: **Y. Senzai:** None. **M. Scanziani:** None.

Poster

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Topic: D.07. Visual Sensory-Motor Processing

Support: UCSF Discovery Fellowship
HHMI

Title: Coordination between nonlocal hippocampal representations and the collicular orienting system

Authors: *C. WILHITE[1], L. M. FRANK[2], M. SCANZIANI[3];
[1]UCSF, SAN FRANCISCO, CA; [2]Departments of Physiol. and Psyciatry, UC San Francisco, San Francisco, CA; [3]Dept. of Physiol., Univ. of California, San Francisco, San Francisco, CA

Abstract: Studies on hippocampal place cells have found neuronal sequences representing nonlocal spatial trajectories that sweep ahead of the animal and orient towards possible left or right future paths. Do these nonlocal orienting sweeps occur in coordination with an orienting command center in the brain? To address this question, we recorded neural activity in the hippocampus and the superior colliculus (SC), a midbrain structure implicated in the control of spatial orienting movements, as mice navigated a Y-maze. We classified hippocampal sweeps based on their directionality and SC neurons based on their turn direction preference on the maze. We discovered that the activity of SC neurons is modulated by a left/right head-body oscillation characteristic of locomotion. Strikingly, SC neurons with opposite direction preferences fire preferentially at opposite phases of the head-body oscillation. Similarly, we found that the onsets of hippocampal sweeps occur in phase with the locomotor head-body oscillation. Notably, the onsets of hippocampal sweeps of opposite directions occur at opposite phases of the head-body oscillation. Lastly, we investigated whether SC neurons fire differently depending on the direction of ongoing hippocampal sweeps. We found that SC neurons fire more during trials that contain sweeps in their preferred direction compared to trials that contain sweeps in their non-preferred direction. Together, our results reveal a coordination between nonlocal hippocampal representations and the SC orienting system.

Disclosures: **C. Wilhite:** None. **L.M. Frank:** None. **M. Scanziani:** None.

Poster

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Topic: D.07. Visual Sensory-Motor Processing

Title: Visual cortex plays a generative role in the plasticity of visually guided orienting behavior

Authors: *E. JONES[1], M. SCANZIANI[2];
[1]Univ. of California San Francisco Neurosci. Grad. Program, San Francisco, CA; [2]Univ. of California, San Francisco, San Francisco, CA

Abstract: Sensorimotor transformations, the process by which sensory inputs are converted into motor commands, are the basis of fundamental behaviors like capturing prey or escaping a threat. The superior colliculus (SC), an evolutionarily ancient brain structure in the visual system, is conserved across vertebrates and is a hub of visuomotor transformations. The superficial layers of the SC contain a retinotopic map of the visual field which is anatomically and spatially aligned with a map of orienting movement vectors contained in the deep layers. The SC exemplifies one strategy with which the brain computes sensorimotor transformations, and the local visuomotor alignment within the SC drives accurate visually guided orienting behavior. For decades, neuroscientists have been fascinated by how sensorimotor alignment is maintained despite an organism's sensory experience changing throughout its lifetime. As such, it is interesting to note that while mammals, like humans and non-human primates, readily adapt to altered visual experiences, evolutionarily older vertebrates, like amphibians, lack this behavioral plasticity. It has been suggested that the evolutionary expansion of cortex in mammals may contribute to this form of adaptation, but direct experimental evidence is lacking. To address this outstanding question, we have developed a novel behavioral paradigm for inducing visuomotor adaptation in freely moving mice that is analogous to paradigms utilized in primates. Our paradigm combines a visually guided orienting task and a novel mouse prism goggle system to shift the visual field. Using this paradigm, we demonstrate for the first time that mice gradually adapt to a chronic shift of their full visual field. Furthermore, we show that lesioning visual cortex (VC) prior to shifting the visual field disrupts normal visuomotor adaptation. Taken together our paradigm reveals that mice have the capacity to adapt to altered visual experience similarly to higher order mammals and suggests that VC may play a generative role in the plasticity of fundamental visually guided behaviors. These findings lend support to the hypothesis that a particular evolutionary benefit of sensory cortex is the generation of experience-dependent behavioral plasticity.

Disclosures: E. Jones: None. **M. Scanziani:** None.

Poster

PSTR026: Cerebellum: Interactions With Other Brain Areas

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.01/F24

Topic: E.02. Cerebellum

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NIH NS113110
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NIH NS132025
McKnight Foundation
Simons Collaboration on the Global Brain

Title: A cerebello-thalamo-cortical pathway supports attractor dynamics in frontal cortex

Authors: *R. GAO, J. ZHU, L. LIU, H. KAKU, N. LI;
Baylor Col. of Med., Houston, TX

Abstract: Before a volitional movement, the brain undergoes a planning phase in which neural activity evolves into a state of readiness for prepared actions. Preparatory activity can be characterized as dynamics that converge to specific activity states, which can be characterized as discrete attractors that correspond to specific subsequent movements. However, the neural circuit substrate supporting these attractors remains unclear. We used Neuropixels probes to map preparatory activity in frontal cortex and thalamus preceding directional licking ("lick left", "lick right") in mice performing a delayed response task. At the level of population activity, preparatory activity was confined to a low-dimensional manifold defined by two activity modes: a choice-selective mode that discriminated lick direction and a non-selective ramping mode that increased to a peak before movement onset. ALM activity along the choice mode predicted upcoming lick direction, even under conditions where ALM activity was optogenetically perturbed. These neural dynamics are consistent with two discrete attractors encoding the two lick directions shaped by an external input (Finkelstein et al 2021; Inagaki et al 2019). In frontal cortex, choice and ramping activity were enriched in anterior lateral motor cortex (ALM). In thalamus, choice and ramping activity were enriched in cerebellar-recipient thalamus, including parts of the ventral-medial nucleus (VM), ventral-anterior-lateral nucleus (VAL), paracentral nucleus (PCN), and central lateral nucleus (CL). The same thalamic regions were also anatomically coupled with ALM, forming a cerebello-thalamo-cortical pathway. To examine cerebellar contribution to the attractor dynamics in ALM thalamo-cortical loop, we photostimulated ChR2 in Purkinje cells to inhibit the cerebellar nuclei. Transient cerebellar perturbation persistently disrupted both choice and ramping modes. A decoder trained on control trial activity could not decode upcoming lick direction after cerebellar perturbation. Notably, a separate decoder trained on perturbed activity could predict lick direction after cerebellar perturbation but not in control trials. The cerebellar perturbation thus disrupted the original attractors and evoked new patterns of persistent activity coding lick directions. These results suggest that attractor dynamics in frontal cortex supporting motor planning is maintained by cerebellar input.

Disclosures: R. Gao: None. **J. Zhu:** None. **L. Liu:** None. **H. Kaku:** None. **N. Li:** None.

Poster

PSTR026: Cerebellum: Interactions With Other Brain Areas

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.02/F25

Topic: E.02. Cerebellum

Support: NIH DIR Funding

Title: All-optical investigation of corticopontine adaptation for cerebellar learning

Authors: *Y. LIU, S. SRINIVASAN, M. J. WAGNER;
NINDS, NIH, BETHESDA, MD

Abstract: The cortico-cerebellar circuit mediates motor and cognitive functions. However, how the cortical activity is propagated through the pontine nuclei (PN), an intermediate layer between the neocortex and cerebellum, remains unclear. Since neurons in the PN are outnumbered by the downstream granule cells (GrCs) by hundreds of times, as well as outnumbered by the upstream neocortical projection neurons, the PN is known as a "bottleneck structure", suggesting the compression of cortical inputs and the expansion coding at the GrC layer. Past work predicted that the cortico-pontine circuit may reweigh the cortical inputs to facilitate the propagation of significant information, enabling the extraction of dominant modes. In this study, via multi-site two-photon microscopy and optogenetics, we are causally testing theories of cortico-cerebellar transmission and adaptation during learning of a forelimb task in mice. Our preliminary results showed the emergence of learning-dependent calcium activity in PN/GrCs. Future work will assess the change of PN/GrCs response to the stimulations of specific cortical neuronal populations. The expected outcome will unravel the circuit mechanism of PN adaptation of cortical inputs, a knowledge gap in the basic science of the study of cortico-cerebellar circuit.

Disclosures: Y. Liu: None. **S. Srinivasan:** None. **M.J. Wagner:** None.

Poster

PSTR026: Cerebellum: Interactions With Other Brain Areas

Location: MCP Hall A

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Program #/Poster #: PSTR026.03/F26

Topic: E.02. Cerebellum

Support: NIH R00 NS110978

Title: Thalamic modes dynamically regulate cerebellar output signals

Authors: *Z. YAO[1], C. CHEN[2];
[2]Neural Behavioral Sci., [1]Penn State Col. of Med., Hershey, PA

Abstract: Cerebellar encoding of movement coordination and control is communicated to the motor cortex through the motor thalamus. The dual firing modes of the thalamic neurons provide a mechanism to dynamically regulate this critical node of information transfer. In burst mode, thalamic neurons fire high-frequency action potentials mediated by low-threshold calcium

currents after a period of hyperpolarization. And in tonic mode, thalamic neurons firing can transfer input more faithfully. Bursting in the thalamus is suggested to occur during slow-wave sleep and in the visual thalamus in awake animals, acting as a “wake-up” call for the cortex. Similar examinations have not been done in the motor thalamus in mice. We performed whole-cell patch clamp in awake-behaving animal in cerebellar receiving territory of the motor thalamus. To investigate thalamic regulation of cerebellar activity, we examined properties of the cerebellar-thalamic synapse using *in vitro* voltage clamp, and simulated DCN activity in stillness and in movement using dynamic clamp. Preparatory activity of the motor cortex in anticipation of specific movements is dependent on this cerebellar-thalamocortical pathway. Therefore, understanding this synapse is critical for decoding the information being transferred from the cerebellum to the cortex.

Disclosures: Z. Yao: None. **C. Chen:** None.

Poster

PSTR026: Cerebellum: Interactions With Other Brain Areas

Location: MCP Hall A

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Program #/Poster #: PSTR026.04/F27

Topic: E.02. Cerebellum

Support: Simons Foundation
NIH Grant R01NS119519

Title: Cerebellar-thalamic interactions during non-motor learning

Authors: *G. M. STINE[1], B. ZHENG[1], M. JAZAYERI[2];
[1]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [2]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: The cerebellum is known to construct internal models that predict the sensory consequences of actions, allowing us to correct errors in ongoing movements and adapt to changes in the environment. An influential hypothesis is that the cerebellum plays a similar role in cognitive function by using internal models to correct and adapt non-motor processes. To test this hypothesis, we developed an interval timing task for monkeys in which animals must use the timing of a predictable stimulus—termed the “flash”—to correct errors in their internal time-keeping and adapt to changes in the temporal environment. In one monkey so far, behavioral data suggest that the monkey forms an internal model to predict the timing of the flash and uses sensory prediction errors to make rapid corrections in its timing behavior within single trials. Moreover, the monkey integrates prediction errors across trials to adapt to blocked changes in the flash time.
To understand whether and how the cerebellum corrects and adapts timing-related signals in the thalamocortical pathway, we performed large-scale recordings in the ventral lateral (VL) thalamus while simultaneously activating the dentate nucleus (DN) with electrical

microstimulation. DN stimulation at the expected time of the flash decreased the monkey's timing variability, mimicking the error-correcting effect of the visual flash. In contrast, DN stimulation at other times within the trial increased variability. We also used DN stimulation to identify the DN-projecting region of VL thalamus. Recording from these neurons in the absence of DN microstimulation, we observed two dominant types of neural activity modulation. The first is a tonic signal whose magnitude tracks the target interval across blocks of trials with different flash times throughout the session. A similar signal has been observed previously and is hypothesized to set the speed of ramp-to-threshold dynamics in sensorimotor neocortical areas needed for motor timing (Wang et al., 2017; Beiran et al., 2023). The second is a ramping signal triggered in response to the flash that ends when the animal initiates its motor response. Ongoing analyses aim to clarify the role of these signals in error correction and adaptation and how DN stimulation modulates thalamic processing.

Disclosures: G.M. Stine: None. **B. Zheng:** None. **M. Jazayeri:** None.

Poster

PSTR026: Cerebellum: Interactions With Other Brain Areas

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.05/F28

Topic: E.02. Cerebellum

Support: NS088567

Title: Network Interactions Among the Hippocampus, Anterior Cingulate Cortex, and Cerebellum During Associative Learning

Authors: *K. BISWAS[1], H. E. HALVERSON[2], J. H. FREEMAN[3];
[1]Univ. of Iowa, IOWA CITY, IA; [2]Iowa Neurosci. Insitiute, [3]Univ. of Iowa, Iowa City, IA

Abstract: The cerebellum is crucial for motor learning and other cognitive functions. Recent evidence suggests the presence of interactions between forebrain structures and the cerebellum, which appears to be involved in a wide range of cognitive processes and associative learning (Halverson et al., 2023). Prior hypotheses for forebrain-cerebellum interactions have primarily posited a unidirectional flow of communication from the forebrain to the cerebellum. However, the potential significance of bidirectional communication in the context of associative learning remains unknown. In this study, we aim to characterize the network activity involved in the dynamic communication between the cerebellum, the anterior cingulate cortex (ACC) and the hippocampus (HPC) throughout the progressive stages of associative learning. We trained Long-Evans rats in trace eyeblink conditioning (tEBC) and simultaneously recorded from the ACC, the HPC and cerebellum using electrophysiology to study local and network activity supporting learning. Preliminary results indicate that the cerebellum and forebrain regions (ACC and HPC) encode the contingency of the conditioned stimulus (CS) and unconditioned stimulus when transitioning from an unpaired pre-training session to the paired training sessions through an

increase in the theta power. When the animal starts to learn, neural activity within the forebrain structures governs the brain's response to the CS, while in the subsequent stages of learning, this role transitions to the cerebellum. Increases in theta and slow gamma power and coherence were found across all three regions following the presentation of the CS, indicating the onset of network activity and intercommunication among the structures as the animal learns. The emergence of strong slow gamma activity in the cerebellum and gamma coherence with the ACC and HPC in the later phases of learning might imply the predominant role of the cerebellum in signaling the forebrain about adaptive timing of the learned response. These findings may explain the presence of a bidirectional interactive network between the cerebellum and the forebrain regions required to drive a wide range of behaviors and cognitive tasks.

Disclosures: K. Biswas: None. **H.E. Halverson:** None. **J.H. Freeman:** None.

Poster

PSTR026: Cerebellum: Interactions With Other Brain Areas

Location: MCP Hall A

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Topic: E.02. Cerebellum

Support: NSF Grant IOS 2128543

Title: Distribution of Cerebellar Projecting Locus Coeruleus (LC) Neurons and Their Dendritic Fields in the Mouse

Authors: *H. K. PREDALE[1], D. J. CHANDLER[1], N. PLUMMER[2], P. JENSEN[2], B. D. WATERHOUSE[1];
[1]Rowan-Virtua Sch. of Translational Biomed. Engin. and Sci., Stratford, NJ; [2]Neurobio., Natl. Inst. of Envrn. Hlth. Sci., Research Triangle Park, NC

Abstract: The brainstem nucleus locus coeruleus (LC) projects broadly throughout the forebrain, brainstem, cerebellum, and spinal cord and is a major source of norepinephrine (NE) release in these regions. While many studies have examined the LC-NE system in rats, there have been fewer systematic investigations of LC afferent and efferent connectivity in mouse. In addition, while we know much about LC organization with respect to sensory and cognitive circuitries and the impact of LC output on sensory guided behaviors and executive function, less is known about LC-NE influences on motor network operations and movement control. To begin closing this gap in understanding, we used a viral-genetic method (TrAC - Plummer et al, 2020) to characterize the anatomy of the mouse LC and its dendritic fields with respect to LC-cerebellar efferent projections. In our model system LC-NE neurons constitutively express tdtomato, allowing visualization of LC-NE soma, dendrites, and axons. As in rat, the mouse LC consists of a core of tightly clustered NE-containing soma surrounded by a dense dendritic field extending 60-800µm into the peri-coerulear space. Dorsally projecting dendrites extend to the 4th ventricle, suggesting direct contact with the cerebrospinal fluid (CSF). The rostral and caudal ends of the LC are

tubular in shape whereas the primary cluster of LC-NE cells is lens shaped along the dorsal-ventral axis. To visualize LC neurons projecting to the cerebellum we Injected CAV2-CMV-Cre into cerebellar terminal fields of our mouse model, causing LC projection neurons to flip their expression from tdtomato to green fluorescent protein. This approach reveals a dense, bilateral distribution of LC cells that send axons to deep cerebellar nuclei (avg=85-180 cells; 68% ipsi, 32% contra) and anterior or posterior cerebellar cortex (avg=53-80 cells; 60% ipsi, 40% contra). Cerebellar projecting LC neurons are concentrated rostro-caudally within the intermediate to ventral 2/3 of the nucleus, with only scattered cells identified in the dorsal LC. These results contrast with the more scattered, sparse, and predominantly ipsilateral (95%) distribution of the NE-containing cells that project from LC to 1° motor cortex. The dendrites of LC-cerebellum projection neurons extend in all directions from the LC core, but with a preference for medial and lateral sub-regions of the peri-coerulear space. These results indicate that: 1) in contrast to other efferent targets, a substantial fraction of LC output is directed to the cerebellum, and 2) this output is driven by inputs to lateral and medial sub-regions of the peri-coerulear space as well as perhaps information transmitted via the CSF.

Disclosures: H.K. Predale: None. **D.J. Chandler:** None. **N. Plummer:** None. **P. Jensen:** None. **B.D. Waterhouse:** None.

Poster

PSTR026: Cerebellum: Interactions With Other Brain Areas

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Topic: E.02. Cerebellum

Support: NS088567

Title: Role of the cerebellum in rule-based category learning and rule-switching in rats

Authors: *S. L. WACHTER, K. L. PARKER, J. H. FREEMAN;
Univ. of Iowa, Iowa City, IA

Abstract: Previous research indicates that humans who have suffer from posterior cerebellar lesions have impaired executive functions such as working memory and task switching (Schmahmann, & Sherman, 1998). In rodents, the posterior hemispheric lobules of the cerebellum have bidirectional communication with frontal cortical areas (i.e., infralimbic, prelimbic, and orbital) via the lateral cerebellar nuclei (LCN). Previous research from our lab showed that bilateral NMDA lesions of the prelimbic area disrupt rule-based category learning. We then hypothesized that cerebellar communication with the prelimbic area might be crucial for rule-based category learning. In the current study, we investigated the role of the cerebellum in ruled-based category learning and rule-switching by disrupting communication between the frontal cortex and the cerebellum with bilateral electrolytic lesions of the LCN (n = 20). Using an operant chamber fitted with a touch screen, rats were presented with a stimulus differing along

two dimensions (spatial frequency and orientation) and were required to categorize each stimulus based on one of the dimensions while ignoring the other, which requires the application of a unidimensional rule (e.g., 'high spatial frequency stimuli are in category A, low spatial frequency stimuli are in category B'). If the rats reached an accuracy criterion of 75% or did not reach the criterion after 30 sessions of training, the relevant dimension (rule) switched and again the rats were trained to either 75% accuracy or 30 sessions. Compared to controls (n = 20), the lesion group took significantly longer to learn the first category rule sand was also impaired after the rule was switched. These deficits emerged without motor deficits, as reflected in reaction times and response rates. To further investigate the role of the cerebellum in categorization, we used an inhibitory DREADDs approach to investigate whether the cerebellum is involved in category learning or performance after learning, with preliminary data indicating that the cerebellum may be involved in learning new category rules.

Disclosures: S.L. Wachter: None. **K.L. Parker:** None. **J.H. Freeman:** None.

Poster

PSTR026: Cerebellum: Interactions With Other Brain Areas

Location: MCP Hall A

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Topic: E.02. Cerebellum

Support: KAKENHI 22H03456
KAKENHI 22H03456

Title: Recovery with forced paralyzed limb use after intracerebral hemorrhage induces switching of motor control systems with kinematic remodeling.

Authors: *S. UENO[1], S. TOMINAGA[1], D. MUSTIKA[1,2], K. KOBAYASHI[3], **H. HIDA**[1,2];
[1]Neurophysiol & Brain Sci., Nagoya City Univ. Grad Sch. Med. Sci., Nagoya, Japan;
[2]Universitas Brawijaya, Faculty of Medicine, Malang, Indonesia; [3]Natl. Inst. Physiol Sci., Okazaki, Japan

Abstract: We have already reported that forced limb use of the paralyzed forelimb (FLU) after intracerebral hemorrhage (ICH) results in functional recovery in the motor executive system, accompanied by switching from the cortico-spinal tract to the cortico-rubral tract (J. Neuroscience 36,455-67:2016). However, it is unknown whether the cerebellum in the motor control system is also accompanied with the switching. To answer this question, we used double viral vector infection method in this study: the involvement of the cerebello-rubral tract was investigated by silencing the pathway from the lateral cerebellar nucleus (AAV-DJ-EF1a-DIO-hM4D(Gi)-mCherry injection) to the parvocellular part of red nucleus (FuG-E-MSCV-Cre injection) with DREADD system. In addition, in order to confirm how the recovered forelimb function is recovered by rehabilitation of FLU, we used DeepLabCut based on deep learning technology to estimate 2D and 3D coordinates, analyzing detail kinematics in ICH group and

ICH + FLU group with and without silencing in the motor control system. Detail kinematics analysis revealed that an inverse correlation between finger opening distance (mean distance between fingertip of index and little finger) and reaching success rate was shown in ICH animals. In addition to significant increase in the success rate, positive relationship between the mean distance and success rate was observed in FLU-ICH group, indicating a qualitative change between ICH injury and FLU-induced rehabilitation. Interestingly, the blockade of the cerebello-rubral tract with clozapine N-oxide significantly reduced the success rate, keeping the positive correlation. Further analysis of the finger shape revealed that the quality of finger movements significantly differs between non-FLU-ICH group and FLU-ICH group. In forelimb reaching movement analysis by DeepLabCut, parameters such as reaching distance and trajectory deviation were deteriorated by ICH. Interestingly, this deterioration was recovered by FLU. These data indicate that kinematic changes occur due to switching of neural circuits in the motor control system as well as the motor executive system

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Poster

PSTR026: Cerebellum: Interactions With Other Brain Areas

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Topic: E.02. Cerebellum

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Israel Science Foundation-1801/18
Israel Science Foundation 1207/23
NIH R01NS105759

Title: The cerebellum facilitates beta-band desynchronization in the motor cortex during reaching movements

Authors: *N. SINHA[1,2], O. BEN HAROSH[1], J. YAO[2], R. HAREL[3], J. P. DEWALD[2], Y. PRUT[1];
[1]Edmond and Lily Safra Ctr. for Brain Sci., Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]Physical Therapy and Human Movement Sci., Northwestern Univ., Chicago, IL; [3]Sheba Med. Ctr., Tel Aviv, Israel

Abstract: Local field potentials (LFPs) in the sensorimotor cortices are dominated by low frequency beta-band oscillations (13-30 Hz). During voluntary movements, power in this frequency band reduces, an event often termed Movement Related beta-band Desynchronization (beta-MRD) indicating an increase in cortical excitability. Previous studies have identified cortico-subcortical networks (chiefly the cortico-basal ganglia loop) as potential sources of beta-MRD. However, the motor thalamus, which is a part of this loop also integrates cerebellar inputs.

In this study, we explored the role of cerebellar-thalamic input to primary (M1) and premotor (PM) cortices on beta-MRD during movements with varying postural demands. Six monkeys were trained to perform a center-out reaching task using their upper limb in two distinct modalities: supported planar-reach (N=4) vs. unsupported free-reach (N=2). The cerebellar outflow was reversibly blocked using high-frequency stimulation (HFS, 130Hz) through an electrode chronically implanted in the superior cerebellar peduncle. Cortical LFPs were recorded while the monkeys performed the tasks with and without HFS. We then performed time-frequency decomposition of M1, and PM LFP activity aligned to the kinematic movement onset to compare changes in beta-MRD during control vs. HFS trials. HFS reduced beta-MRD in M1 by 15% ($p = 0.005$) during supported reaching and 13% ($p = 0.006$) during free-reaching. The effect of HFS was significantly stronger on beta-MRD for free-reaching movements to higher targets (18% reduction, $p = 0.003$), which required the monkeys to lift the weight of the upper limb against gravity, as compared to lower targets (8% reduction, $p = 0.034$) in the free-reaching task. In PM, HFS reduced beta-MRD by 12% ($p = 0.016$) only during the movements to higher targets in the free-reaching task, likely due to the role of PM in generating postural drive during such movements. Our findings thus indicate that intact cerebellar signals enhance movement-related beta-MRD in the motor and premotor cortices. Additionally, its effect is contingent on both the motor cortical area and the postural requirement of the reaching task.

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Poster

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Topic: E.02. Cerebellum

Support: NS050808
DA044761
MH115604
RR027888

Title: Exploring the role of cerebellar modulation of prefrontal dopamine in behavioral flexibility

Authors: *J. VERA, M. ONATE, C. CHEN, L. SPAETH, K. KHODAKHAH;
Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: The cerebellum (Cb) has been associated with mental disorders related to dopamine (DA) dysregulation in medial prefrontal cortex (mPFC), such as schizophrenia and autism. However, how the Cb contributes to DA signals in the mPFC remains to be established. Cortical DA encodes stimulus salience, reinforces rewarding actions, and is required for flexible

behavior. Cortical DA is provided by projections from the ventral tegmental area (VTA), a key region of the brain reward system. We have established the anatomical and functional properties of the Cb->VTA->mPFC circuit in the mouse brain, finding that neurons from all three nuclei of the Cb monosynaptically contact VTA neurons that project to mPFC, and that activation of Cb inputs to VTA drives a fast (ms time scale) rise in the firing rate of ~80% of mPFC neurons together with a slow (seconds time scale) increase in dopamine levels. To explore the behavioral role of this circuitry we are using a reward-based decision-making task modified from the task implemented by the IBL. Head-restrained mice learned to use their front paws to steer a wheel that controlled the position of a visual cue displayed in the center of a digital screen placed in front of them. Mice needed to move the visual cue to one of the borders of the screen to receive a water reward. At each trial movements toward only one side were considered correct and rewarded (left or right), while movements to the opposite side triggered an error sound cue. The rewarded side was reversed when mice reached >80% correct responses. After 9 days of training mice fully learned the reversal task and reached a plateau performance of >10 rule reversals per session. Inactivation with muscimol or block of DA receptors in the mPFC biased action selection, reduced correct responses to less than 50% and made the mice incapable of successfully implementing rule reversal. Intriguingly, inactivation of the cerebellar vermis had comparable effects. These preliminary results support the hypothesis that Cb and mPFC are required for rule reversal, and that DA signaling in mPFC contributes to behavioral flexibility. We are performing additional experiments to selectively manipulate the different components of the circuitry to thoroughly test this hypothesis.

Disclosures: J. Vera: None. **M. Onate:** None. **C. Chen:** None. **L. Spaeth:** None. **K. Khodakhah:** None.

Poster

PSTR026: Cerebellum: Interactions With Other Brain Areas

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Program #/Poster #: PSTR026.11/F34

Topic: E.02. Cerebellum

Support: NS050808
DA044761
MH115604
RR027888

Title: Anatomical organization of the cerebellar inputs to the midbrain dopamine centers and their disynaptic targets

Authors: *M. OÑATE, J. VERA, L. KHATAMI, K. KHODAKHAH;
Albert Einstein Col. of Med., Bronx, NY

Abstract: The cerebellum is involved in a wide range of functions from motor control to cognitive behaviors and its dysfunction is associated with a variety of pathologies ranging from motor diseases such as Dystonia and Parkinson's to behavioral and mental disorders such as addictive behavior, obsessive-compulsive disorder, schizophrenia, and autism spectrum disorder. Our laboratory has previously shown that the cerebellum (Cb) sends direct excitatory projections to the midbrain dopamine neurons in the ventral tegmental area (VTA), Cb-VTA, and the substantia nigra pars compacta (SNc), Cb-SNc. Optogenetic activation of these specific projections results in dopamine release in downstream targets in the medial prefrontal cortex (mPFC), nucleus accumbens (NAc) and in the dorsal striatum (DS), respectively. Moreover, behavioral experiments in mice suggest that dopamine modulation by the Cb-VTA projection activates reward circuits and promotes social preference, while the Cb-SNc projections may promote movement vigor. Yet, little is known about the anatomical details of these projections. Using different intersectional anatomical tracing experiments, we explore the organization of the specific sub-circuits. We find that all three deep cerebellar nuclei (DCNs) contribute to cerebellar projections to the VTA and SNc, and both arise from similar regions in each DCN nuclei. Analysis of the laterality of the projections suggests that while cerebellar projections to these nuclei are bilateral, projections to SNc are mainly contralateral, while projections to VTA are more equilateral. Furthermore, all three DCNs send disynaptic projections (via the VTA) throughout all the mPFC and NAc, and (via the SNc) to the medial and lateral DS. Retrograde tracing experiments in NAc and DS show that different regions of each nucleus are targeted by different VTA and SNc neurons, respectively, which seem to originate from predominantly different groups of neurons in the DCNs. On the question of whether cerebellar midbrain projections arise as collaterals of the same output axons or if they are distinct projections, preliminary results suggest that Cb-VTA and Cb-SNc projections emerge primarily from different populations of neurons, forming different sub-circuits. Thus, cerebellar projections appear to provide specific and distinct connections to different dopamine pathways through different set of neurons targeting the basal ganglia and the cortex, suggesting differential cerebellar modulation of the dopamine pathways in the brain involved in motor and non-motor behaviors.

Disclosures: **M. Oñate:** None. **J. Vera:** None. **L. Khatami:** None. **K. Khodakhah:** None.

Poster

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NIMH Grant R01MH115604

Title: Exploring monosynaptic midbrain-to-deep cerebellar nuclei projections

Authors: *J. GUARQUE-CHABRERA, M. OÑATE, J. VERA, K. KHODAKHAH;
Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: Classically implicated as primarily involved in coordinating high computational motor tasks, emerging evidence has unveiled the cerebellum's involvement in a large variety of non-motor behaviors. These include tasks associated with fear memory, cognitive flexibility, goal-directed behavior, rewarded behavior, and emotional processing. Moreover, several findings implicate cerebellar dysfunction in neuropsychiatric conditions such as autism, obsessive-compulsive disorder, depression, schizophrenia, and substance use disorders. Direct and indirect ascending cerebellar pathways modulate the activity of diverse brain regions such as the medial prefrontal cortex, limbic areas, basal ganglia, midbrain, and the nucleus accumbens. Descending pathways, on the other hand, provide input to the cerebellum, and in this context, inputs via the pontine nuclei have received the bulk of the attention, sidelining extra-pontine cerebro-cerebellar pathways.In recent years extensive interactions between the cerebellum and the midbrain have been revealed. Monosynaptic deep cerebellar nuclei (DCN)-to-midbrain projections have been described and implicated in regulating rewarded behaviors. However, whether a reverse midbrain-to-cerebellum connection exists remains an open and hotly debated question. We have used extensive neuro-anatomical tracing approaches and fiber photometry to explore the presence and utility of direct midbrain-to-DCN projections. To create an anatomical map of the midbrain input neurons that monosynaptically project to each of the deep cerebellar nuclei, we injected the retrograde tracers fluorogold or AAVrg-*cre* virus into each of the three deep cerebellar nuclei of wild-type and RCE mice respectively. To explore whether some midbrain projection neurons were dopaminergic, we injected a *cre*-dependent herpes virus in the midbrain of DAT-*cre* mice. Interestingly, our neuroanatomical data suggest that all three DCN receive monosynaptic dopaminergic projections from the midbrain. Moreover, we find that the midbrain neurons that target different deep cerebellar nuclei have differential topographic distributions in the midbrain, suggesting that all deep cerebellar nuclei do not receive the same information from the midbrain. Given the extent and the diversity of the projections from the midbrain to the cerebellum, we are using fiber photometry and dopamine indicators to explore the efficacy of these projections in increasing cerebellar dopamine levels and the nature of the information that the midbrain conveys to the cerebellum under diverse behavioral paradigms.

Disclosures: J. Guarque-Chabrera: None. **M. Oñate:** None. **J. Vera:** None. **K. Khodakhah:** None.

Poster

PSTR027: Bimanual Coordination and Other Motor Control

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.01/F36

Topic: E.04. Voluntary Movements

Support: NSF Grant 1934792

Title: Kinematic changes and neural correlates of bimanual coordination when synchronizing distinct motor functions

Authors: *A. KANAPSKYTE[1], W. ZHOU[2], J. A. GARCIA ARANGO[3], K. HONG[4], J. SCHOFIELD[5], L. M. MILLER[4], S. S. JOSHI[6], W. M. JOINER[7];
[1]Univ. of California, Davis, Davis, CA; [2]Neurobiology, Physiol. and Behavior, Univ. of California Davis, Davis, CA; [3]Univ. of Washington, Seattle, WA; [4]Univ. of California Davis, Davis, CA; [5]Mechanical and Aerospace Engin., UC Davis, Davis, CA; [6]Mechanical and Aerospace Engin., Univ. of California, Davis, Davis, CA; [7]Dept. of Neurobio., Physiol. and Behavior, Univ. of California, Davis, Davis, CA

Abstract: Unlike unimanual limb control, coordinated bimanual motor control has not been well characterized. In numerous bimanual tasks (e.g., opening a jar of peanut butter), the motor functions of the two hands are distinct but complementary, having unique spatial and temporal profiles. To further advance our understanding of coordination we measured brain activity with electroencephalography (EEG) while participants completed a novel bimanual task that prompted the user to enact two different, but complimentary motor functions. Participants used one hand to control the orientation of a rectangular screen cursor and the other hand to control the two-dimensional cursor trajectory. We introduced visual feedback perturbations to each motor function (reach or rotation) that either increased or decreased the corresponding changes in the cursor's trajectory or orientation by 25%. The experiment started with 220 familiarization trials (practicing each motor function separately and then together), followed by 128 baseline trials, 100 training trials with a visual feedback perturbation applied to only one limb, and finally 224 generalization trials in which subjects repeated 4 trials with visual feedback followed by 3 trials without visual feedback. After this, each subject repeated the experiment again with the same visual feedback perturbation applied to the opposite limb. Preliminary results (N=23 participants) suggest that perturbing the trajectory feedback under control of one limb affected the other, unperturbed limb. However, this subsequent modulation of the unperturbed limb was not observed for perturbing the orientation feedback. Furthermore, analyzing the brain activity during familiarization with the coordination paradigm, we observed desynchronization of neuronal populations across the alpha (8-12 Hz) and beta (12-30 Hz) frequency bands interhemispherically, confirming previous literature in which desynchronization has been noted to correspond to movement planning, initiation, and/or completion. Although preliminary, these results suggest that dependent on the required motor function (fine versus more course recalibration), adaptation of bimanual coordination may be asymmetric, with corresponding differences in the underlying neural activation patterns.

Disclosures: A. Kanapskyte: None. **W. Zhou:** None. **J.A. Garcia Arango:** None. **K. Hong:** None. **J. Schofield:** None. **L.M. Miller:** None. **S.S. Joshi:** None. **W.M. Joiner:** None.

Poster

PSTR027: Bimanual Coordination and Other Motor Control

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Program #/Poster #: PSTR027.02/F37

Topic: E.04. Voluntary Movements

Title: Contributions of strength and corticospinal tract integrity to agility in aging humans

Authors: *E. G. MACKENZIE, N. W. BRAY, S. Z. RAZA, M. E. PLOUGHMAN;
Med., Mem. Univ. of Newfoundland, St. John's, NL, Canada

Abstract: Introduction: Agility describes the ability to change the body's position quickly, requiring a combination of balance, coordination, muscle strength and endurance. As such, agility requires contributions by the neuromuscular system, inclusive of the corticospinal tract (CST), and skeletal muscle. Traditionally, agility tests are reserved for high-performance athletes and leverage a simple stopwatch, ignoring spatiotemporal parameters and an aging demographic; this is interesting considering agility is critical for preventing falls, age-related physiological changes begin as early as the fourth decade. We developed a novel propulsive bipedal hopping test performed on an instrumented walkway. We aimed to determine whether quadriceps strength or CST integrity predicted agility performance. **Methods:** We recruited 32 community-dwelling subjects, 30+ years of age. We used active motor threshold, assessed via transcranial magnetic stimulation, as a measure of CST integrity. An isometric knee extension, measured via a handheld dynamometer, recorded leg muscle strength. We assessed agility via a hopping task along a walkway capable of recording spatiotemporal properties; the hopping task required participants to hop from one end and back as fast as possible. Spatiotemporal measures of interest included hop length (cm) and hop length variability. We used regression modelling to predict the individual contribution of quadriceps strength and CST integrity to each spatiotemporal property whilst controlling for sex. **Results:** As expected, older age relates to shorter hop length (r = -.671, p <.001), and greater hop length variability (r =.423, p =.016). Reduced leg strength predicted hop length ($R2$ =.393, p =.002) but not hop length variability. Conversely, CST integrity predicted hop length variability ($R2$ =.182, p =.036) but not hop length. **Conclusion:** The agility test revealed age-related differences in muscular and nervous system properties, suggesting that the propulsive bipedal hopping test may serve as a sensitive clinical measure for uncovering subtle age-related changes in the neuromuscular system. Further, our findings indicate that unique physiological factors are more or less responsible for specific components of hopping and, by extension, agility. Specifically, leg strength was critical to agility strength, as reflected by hopping length, while CST integrity was critical to agility coordination and consistency, as reflected by hopping variability.

Disclosures: E.G. MacKenzie: None. **N.W. Bray:** None. **S.Z. Raza:** None. **M.E. Ploughman:** None.

Poster

PSTR027: Bimanual Coordination and Other Motor Control

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Program #/Poster #: PSTR027.03/G1

Topic: E.04. Voluntary Movements

Title: Changes in movement variability with learning for precision tasks

Authors: *N. SHIN, R. RANGANATHAN;
Kinesiology, Michigan State Univ., East Lansing, MI

Abstract: Discrete tasks requiring precision in movement outcome (like a dart throw) require minimizing motor variability at a specific instant of time (i.e., the point of release). However, because movements unfold in time, understanding how motor variability is modulated in time throughout the movement, and how redundant solutions are exploited is critical. The purpose of the study is to understand how motor variability changes with practice during the practice of a redundant task. 40 participants learned a bimanual shuffleboard task where the goal was to slide a virtual puck towards a target. This required participants to release the puck at a consistent speed by using both hands. All participants practiced with the same target for 12 blocks of 25 trials, and the retention of learning was tested after 24 hours. Results showed that (i) velocity profiles changed with practice, with the release point moving to regions of lower accelerations, and (ii) motor variability decreased with practice - however, this decrease was only observed in the movement variability that affected task performance. These results suggest that with learning, participants develop error-tolerant strategies that minimize the effect of motor variability on task performance.

Disclosures: N. Shin: None. **R. Ranganathan:** None.

Poster

PSTR027: Bimanual Coordination and Other Motor Control

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.04/Web Only

Topic: E.04. Voluntary Movements

Support: Department of Science and Technology, Government of India

Title: Flexible bimanual coordination through task-dependent feedback control

Authors: P. RAVIKUMAR, A. SAHU, ***P. MUTHA**;
Indian Inst. of Technol. Gandhinagar, Gandhinagar, India

Abstract: The coordination of symmetric bilateral arm movements is thought to be mediated via shared motor commands to homologous sets of muscles in both arms. However, recent work (e.g., Kitchen et al., 2023) has argued that the two arms can be independently or codependently controlled based on each arm's contribution to the achievement of the task goal. Kitchen et al. found that when each arm's contribution to the perpendicular motion of a shared feedback cursor was differentially altered during forward reaching, motor variability in the arm with the higher contribution was curtailed, while the other arm was allowed to vary more freely, pointing to task-dependent modulation. However, it is unclear whether: 1) such modulation occurs when each arm's contribution to the more task-relevant, parallel (forward) motion of the cursor is

differentially varied, and 2) the sensorimotor system can resolve simultaneously imposed alterations in the perpendicular and parallel directions. To address this, we employed a bimanual shared cursor reach task in which visual feedback was altered by changing each arm's contribution to the cursor's perpendicular and/or parallel position. Replicating Kitchen et al., we first found that if an arm contributed more to the perpendicular motion of the cursor, its variability in that direction was restricted compared to the arm that contributed less. In exp 2, when we altered each arm's contribution to the parallel motion of the cursor, we again found a reduction in variability of the arm with the higher contribution to cursor motion and increased variability in the other, but in the parallel direction. In exp 3, we changed the contributions in the perpendicular and parallel directions simultaneously: one arm contributed more to perpendicular and less to parallel cursor motion, while the other had opposite contributions. In exp 4, the same arm contributed more to both perpendicular and parallel cursor motion, while the other contributed less in both directions. Notably, we found that irrespective of the gain combinations, the arm with the higher perpendicular contribution showed reduced lateral variability and the arm with the higher parallel contribution demonstrated restricted parallel variability, while allowing the corresponding lower contribution arms to compensate for the shared cursor errors. Thus, the sensorimotor system always appeared to prioritize corrections for deviations directly impacting task goals (higher contribution arm), while tolerating more variability in less relevant dimensions (lower contribution arm). This study adds to the growing body of evidence supporting task-dependent control in bimanual coordination.

Disclosures: **P. Ravikumar:** None. **A. Sahu:** None. **P. Mutha:** None.

Poster

PSTR027: Bimanual Coordination and Other Motor Control

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Topic: E.04. Voluntary Movements

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ReproRehab Program (NIH NICHD/NCMRR Grant #R25 HD105583)

Title: Fine motor deficits in early Parkinson's Disease differ based on initial symptom onset side and distinct task component

Authors: J. MANNING[1], **C. SELB**[1], M. BARRETT[2], P. E. PIDCOE[3], *B. DEXHEIMER[1]; [1]Occup. Therapy, Virginia Commonwealth Univ., Richmond, VA; [2]Neurol., Virginia Commonwealth Univ., Richmond, VA; [3]Physical Therapy, Virginia Commonwealth Univ., Richmond, VA

Abstract: Cardinal Parkinson's Disease (PD) motor symptoms, such as tremor, bradykinesia, and rigidity, often manifest unilaterally in early stages. Our on-going study aims to characterize

these early motor deficits while considering the underlying lateralized specializations of each hand. We have hypothesized that early PD motor deficits differ in functional impact based on initial symptom onset side (dominant vs. non-dominant) and distinct task component (trajectory control vs. robust stabilization), due to lateralized motor control mechanisms. Our preliminary dataset includes nine right-handed individuals with early PD (Hoehn & Yahr Scale 1 or 2). We characterized symptom severity via Part III of the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS). We grouped participants as primarily right-PD (n = 7) or left-PD (n = 2) based on total right-minus-left difference scores. The groups did not differ in rigidity and bradykinesia scores, but the right-PD group showed a trend towards higher tremor scores (p = .061). Total Part III scores did not differ between the groups. Individuals performed a tablet-based bimanual fine motor task. One hand stabilized a stylus over a stationary target, while the other hand moved a second stylus to on-screen targets. The two styluses were connected by a tension band to mimic mechanical forces that may arise during everyday bimanual tasks. We quantified reaching component performance via mean stylus deviation from the linear path to each target and stabilizing component performance via mean stylus displacement from the stationary target. Our pilot findings show distinct performance differences between the groups. For the reaching component, both groups performed better overall with their right hand vs. their left (p = .016), despite this being the more affected hand in the right-PD group. For the stabilizing component, the right-PD group performed worse with their right hand vs. their left (p = .001), while the left-PD group performed similarly with each hand (p = .59), despite their left hand being more affected vs. their right. When correlating symptom severity with performance, we observed several trends approaching significance. More severe tremor scores, regardless of group, appeared to predict *better* reaching component performance (r^2 = .43; p = .054), while more severe rigidity scores, regardless of group, appeared to predict *worse* reaching component performance (r^2 = .38; p = .080) and *better* stabilizing component performance (r^2 = .39; p = .070). Data collection for this study remains on-going, but these preliminary findings suggest that left- and right-PD symptoms differentially affect fine motor deficits.

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Poster

PSTR027: Bimanual Coordination and Other Motor Control

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Program #/Poster #: PSTR027.06/G3

Topic: E.04. Voluntary Movements

Support: NSF 1553895

Title: Different but complimentary motor functions reveal an asymmetric recalibration of upper limb bimanual coordination

Authors: *W. ZHOU[1], A. KANAPSKYTE[2], K. HONG[3], L. M. MILLER[4], S. S. JOSHI[3], J. SCHOFIELD[3], W. M. JOINER[4];
[1]Univ. of California Davis, Davis, CA; [2]Dept. of Biomed. Engin., Univ. of California, Davis, Davis, CA; [3]Dept. of Mechanical and Aerospace Engin., Univ. of California, Davis, Davis, CA; [4]Dept. of Neurobio., Physiol. and Behavior, Univ. of California, Davis, Davis, CA

Abstract: Bimanual coordination, a fundamental aspect of human motor control, typically involves the execution of different functions by the two limbs. Assessing bimanual coordination is complex, as it requires consideration of both the spatial and temporal properties of movement. Previous research has largely investigated bimanual control through simple coordination tasks in which the limbs perform similar movements (e.g., finger tapping). However, few studies have specifically examined coordination when the two limbs perform different yet complementary functions. Here we investigated the spatiotemporal coordination of the two limbs performing different motor functions, and subsequently determined the relative changes in the respective motor behaviors when visual perturbations were applied. Four groups of participants were recruited to participate in 4 separate experiments, each employing the same paradigm but involving different visual feedback perturbations. Participants performed 10 cm point-to-point reaching movement to move a rectangular cursor using one limb while rotating a knob to match the orientation of the goal target using the other limb. Subjects completed 90 baseline trials, 100 training trials with the visual feedback gain perturbation (either increasing or decreasing by 25% the visual feedback of the cursor trajectory or orientation), and 45 washout trials. Results showed rapid adaptation to perturbations in visual feedback of the movement trajectory, affecting both the perturbed limb controlling object trajectory and the unperturbed limb controlling object orientation. By the end of training, significant differences emerged between the trajectory gain increase and decrease groups (reaching amplitude, duration, and peak velocity, $P < 0.001$ for all cases), that persisted during early phase of the washout period. Conversely, perturbation to the visual feedback of orientation primarily only influenced the perturbed limb controlling orientation (rotation duration and peak velocity, $P < 0.011$), with minimal impact on movement trajectory parameters ($P > 0.05$). In addition, through cross correlation, we assessed the temporal coordination between the two limbs and found perturbations in visual feedback of movement trajectory led to significant changes in limb coordination, whereas no notable difference was observed for perturbations of orientation. These findings indicate asymmetries in the motor recalibration dependent on the perturbed aspect of visual feedback (orientation vs. trajectory), suggesting possible differences in the underlying neural mechanisms and inter-hemisphere communication.

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Poster

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Topic: E.04. Voluntary Movements

Support: NIH Grant R01EB03125
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Title: Coordination-dependent haptic feedback based on real-time bimanual geometric features improves skill acquisition in robot-assisted surgical training

Authors: J. BOEHM[1], *N. FEY[2], A. MAJEWICZ FEY[2];
[1]Univ. of Heidelberg, Heidelberg, Germany; [2]The Univ. of Texas at Austin, Austin, TX

Abstract: Bimanual coordination is a feature of human motor behavior critical to many tasks of daily living and vocational-specific activities. In robotic surgery, for example, trainees must learn to use both hands in a simultaneous and coordinated manner to perform complex tissue manipulation tasks such as suturing, ablation, dissection etc. However, these complex motions are not always easy to perform or intuitive to understand. Therefore, a system capable of measuring bimanual coordination in an online way could be coupled with haptic feedback strategies to accelerate motor learning. In this work, we construct a framework based geometric analysis of real-time kinematic data to classify various types of bimanual coordination modes including motion sequence, scaling, direction, and symmetry. In a randomized control trial with 10 human subjects, adaptive haptic feedback was applied based on the sequence and symmetry of the right and left hand of the subject while performing a peg transfer surgical training task using the da Vinci Research Kit surgical robot. To ensure significant results, all subjects performed the peg transfer tasks for a total of 14 times, 2 for familiarization and a base-line pre-test, then 8 times total with or without haptic feedback, based on random assignment to the groups, and finally 4 additional times for a washout trial and post-test without haptic feedback for all subjects. Baseline scores in the pre-test showed no significant differences between groups but subjects in the group receiving adaptive haptic feedback had significantly better performance improvement over the control group ($p = 0.008$) including their total task time and # of blocks dropped. When analyzing the motions after the experiment, we found the haptic feedback subjects also had significantly more simultaneous bimanual motion in post-test, likely due to the haptic guidance received during the training portion of the experiment. Overall, this work shows that by monitoring the geometrical features of bimanual coordination and associating those motions with online guidance, we can improve bimanual coordination and even show lasting augmentation to performance for challenging bimanual motor tasks.

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Poster

PSTR027: Bimanual Coordination and Other Motor Control

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Title: Dynamic changes in interlimb transfer during real-world motor skill learning

Authors: *C. YIN, Y. WANG;
Capital Univ. of Physical Educ. and Sports, Beijing, China

Abstract: Interlimb transfer in motor learning has been studied extensively in a variety of disciplines, including psychology, kinesiology, neuroscience, and engineering. However, it is unknown whether the amount of transfer can be improved with more training and passage of time. Here, we examined the dynamic changes in interlimb transfer in a laser pistol shooting task. Thirty-six right-handed participants were trained with either the right or left hand on two consecutive days. Before and after training, they were randomly tested with both hands. Shooting accuracy was the primary variable of interest in assessing final performance. They did not show significant improvement during each training phase, but training performance on the second day was significantly better than on the first day for both groups. Importantly, the left-hand performance improvement for the right-hand training group was similar to that of the left-hand training group for all three tests on the two training days. However, the right-hand performance improvement for the left-hand training group was much less than that for the right-hand training group for all three tests on the two training days. This means that the transfer is not symmetrical: the amount of transfer from the left hand to the right hand is much smaller than that in the opposite direction. Specifically, we found that there was no transfer from the left to the right hand after training on the first day. Surprisingly, however, there was a transfer before training on the second day, although it was smaller than the transfer from the right to left. This finding suggests that the magnitude of interlimb transfer is not monotonous, but changes over time. In addition to providing important insights into how the two hemispheres of the brain communicate with each other, the study may also have implications for the rehabilitation of unilateral motor impairments.

Disclosures: C. Yin: None. **Y. Wang:** None.

Poster

PSTR027: Bimanual Coordination and Other Motor Control

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Title: Quantitative and qualitative analysis of the callosal connectivity in the macaque brain.

Authors: M. RIZZO, G. LUPPINO, *E. BORRA;
Med. and Surgery, Univ. di Parma, Parma, Italy

Abstract: In the macaque brain most cortical areas are connected through the corpus callosum to the same or different areas of the contralateral hemisphere (homotopic and heterotopic callosal connections). Several studies have already focused on the distribution of the callosal connectivity of different cortical areas, but quantitative data on the proportion of their contra- vs. ipsilateral afferences and, except for premotor areas, on the relative distribution of homotopic vs. heterotopic connections is still lacking. In the present study, we analyzed qualitatively and quantitatively the distribution of retrogradely callosal labeled neurons (CLN) after neural tracer injections in parietal and prefrontal areas (23 tracer injections in 12 macaques). The results first showed that the percentage of CLN varied across the different studied areas. Specifically, for areas MIP and PEip of the superior parietal lobule (SPL) CLN were about 10%. A similar contribution was observed for the two caudal inferior parietal (IPL) areas Opt and PG and for the intraparietal area AIP, whereas for the rostral IPL areas PFG and PF the percentage of CLN was quite low. In the dorsolateral prefrontal (DLPF) cortex, rostral area 46d showed a very high percentage of CLN (26%) whereas in the intermediate and caudal 46d it was about 10%. Finally for the ventrolateral prefrontal (VLPF) cortex the percentage of CLN was relatively higher with respect to the other studied regions. Second, for SPL areas homotopic connectivity was only 20-30% of the total number of CLN and heterotopic connections were relatively widespread involving mostly SPL, but also IPL, frontal motor, and cingulate areas. For IPL areas the percentage of homotopic CLN was higher (30-60%) and heterotopic connections involved mostly other IPL areas, plus caudal SPL and cingulate areas for Opt and PG and rostral SPL areas and area 24 for AIP and PFG. DLPF areas showed a very high percentage of homotopic CLN (50-60%) and heterotopic connections with frontal oculomotor areas for caudal 46d and dorsal premotor areas for intermediate 46d. Finally, rostral VLPF injections showed a low homotopic connectivity and a strong heterotopic one mostly with other VLPF and orbitofrontal areas, whereas more caudal VLPF areas showed a relatively high homotopic connectivity and heterotopic connections with the ventral premotor cortex. The present study is the first in providing a quantitative evaluation of the callosal connectivity in the macaque brain and represents a first step toward a more comprehensive description of a connectional feature, which appears relevant for most cortical areas.

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Poster

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Title: Pulling the Strings on Behavior: Space Radiation and Social Isolation Impact on Motor Control

Authors: *K. S. DHEDE[1], K. D. OMENGAN[2], S. L. GLEED[2], T. L. GARCIA[2], A. A. BLACKWELL[2];
[1]Psychology, Univ. of Nevada, Las Vegas Neurosci. Grad. Program, Las Vegas, NV;
[2]Psychology, Univ. of Nevada, Las Vegas, Las Vegas, NV

Abstract: Deep space exploration poses unique challenges that may compromise astronaut health and operational readiness. Among the most concerning challenges are exposure to unavoidable galactic cosmic radiation (GCR) and prolonged periods of social isolation inherent to long-duration missions. However, the combined impact of these factors on mission-relevant sensorimotor capabilities remain poorly characterized. We investigated the individual and combined effects of a single low dose of Helium (10 cGy at 250 MeV/n delivered ~6 months of age), one ion that comprises simulated GCR and 24 days of social isolation on fine motor skills in adult outbred Wistar rats (n=44) using a string-pulling task. This task requires rats to reach for, grasp, and pull a string to obtain a reward tied at the end. Three months following radiation exposure at ~9 months of age, approximately half of the rats were exposed to isolated or pair-housed conditions. String-pulling performance was assessed across four days prior to isolation, for two days midway through, and at the end (days 21-24). Repeated measures ANOVAs revealed that radiation and isolation produced sensorimotor impairments that varied across days and by sex. On the final test day, male irradiated rats exhibited greater missed attempts to grasp the string relative to male shams. All isolated rats exhibited decreased fine motor control, making more missed attempts to grasp the string, particularly on day 21 of isolation relative to day 24. Notably, irradiated isolated rats showed the most pronounced deficits in the ability to grasp the string with their mouth, suggesting an additive effect of these stressors, on day 21 of isolation compared to day 24. Sex differences were also observed, with male rats demonstrating greater hand misses following irradiation and more mouth misses after irradiation and isolation combined on day 21 relative to 24. In addition, overall, male rats engaged in more mouth misses than females. These findings indicate that Helium exposure and social isolation independently and synergistically impair rat sensorimotor performance depending on sex and test day; many deficits were reduced with additional exposure to string-pulling suggesting that this task may be used as a behavioral assessment and potential countermeasure. This work may have implications for astronaut health and operational capabilities during long-duration spaceflight.

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Poster

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Title: The topography of cortical muscle control and temporal coordination in the Egyptian fruit bat (Rousettus aegyptiacus)

Authors: *M. HAFEZI[1,2], J. LIGGINS[3], A. C. HALLEY[4], C. R. PINEDA[5], T. A. SCHMID[6], F. GOMEZ[5], R. BOPARAI[4], S. HOSSEINI[3], L. A. KRUBITZER[5,7], M. M. YARTSEV[8,9], D. F. COOKE[3,2];
[1]Simon Fraser Univ., Vancouver, BC, Canada; [2]Institute for Neuroscience and Neurotechnology, Simon Fraser University, Burnaby, BC, Canada; [3]Biomed. Physiol. and Kinesiology, Simon Fraser Univ., Burnaby, BC, Canada; [4]Ctr. for Neurosci., Univ. of California Davis, Davis, CA; [5]Psychology, Univ. of California Davis, Davis, CA; [6]Helen Wills Neurosci. Inst., California Clin. Trials, Berkeley, CA; [7]Center for Neuroscience, University of California Davis, Davis, CA; [8]Neurosci., UC Berkeley, Berkeley, CA; [9]Bioengineering, UC Berkeley, Berkeley, CA

Abstract: Most natural behaviors require the coordination of muscles distributed across the body. Among neural structures involved in motor control, the neocortex plays a major role in coding movements involving multiple muscles. Intracortical microstimulation (ICMS) delivered to the sensorimotor cortex (e.g. M1, parietal areas) can evoke multijoint movements that closely match behaviors like feeding and reaching that are necessary for survival. How does the neocortex coordinate the activation of diverse muscles across the body to produce an adaptive motor response? We explored the topography and temporal patterns of muscle representations in four Egyptian fruit bats (Rousettus aegyptiacus), which, like other members of Chiroptera, have evolved several behaviors unique to mammals, including self-propelled flight, lingual clicks used for echolocation, and complex vocal social communication. We used a combination of long-train ICMS and electromyography (EMG) across 16 muscles in the face, forelimb, torso, and hindlimb, focusing on muscles involved in flight (including occipito-pollicalis, which is unique to bats), echolocation (several tongue muscles and mouth and jaw muscles), and complex social communication (cricothyroid muscle of the larynx). To extract temporal features from evoked muscle activity (i.e. onset, offset, and duration), we use a custom machine learning algorithm. We are developing an addition to our algorithm to identify topographic functional clusters of temporal muscular coordination that could be linked to specific behaviors like echolocation and

flight. We found that representations of single muscles are broadly overlapping and many spanned motor and somatosensory cortex. Some muscles exhibited topographical differences in ICMS-evoked EMG waveforms (as we previously showed in rats). For example, the medial cricothyroid representation in the motor cortex exhibited activity lasting hundreds of milliseconds, while EMG activity evoked from lateral sites in the somatosensory cortex comprised 1-2 spikes as brief as 20 ms. Our feature analysis revealed that onset, offset and duration of activity for many muscle representations varied systematically across the cortex and the relative timing of coactivating muscles varied across sites. Moving forward, we will use our clustering algorithm to explore the topography of more complex evoked EMG patterns.

Disclosures: **M. Hafezi:** None. **J. Liggins:** None. **A.C. Halley:** None. **C.R. Pineda:** None. **T.A. Schmid:** None. **F. Gomez:** None. **R. Boparai:** None. **S. Hosseini:** None. **L.A. Krubitzer:** None. **M.M. Yartsev:** None. **D.F. Cooke:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.01/G9

Topic: I.08. Methods to Modulate Neural Activity

Support: JSPS KAKENHI Grant Number 23H03416
JSPS KAKENHI Grant Number 21K19755
Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering
Suzuken Memorial Foundation

Title: In vivo bidirectional modulation induced by localized theta-burst magnetic stimulation to the mouse auditory cortex

Authors: *T. YOSHIKAWA[1], T. TATENO[2];
[1]Grad. Sch. of Information Sci. and Technol., Hokkaido Univ., Sapporo, Hokkaido, Japan; [2]Fac. of Information Sci. and Technol., Hokkaido Univ., Sapporo, Hokkaido, Japan

Abstract: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method used to treat neurological and psychiatric disorders. Theta burst stimulation (TBS) is a form of rTMS, in which 50 Hz triplet pulses are delivered at 5 Hz. TBS has attracted interest because of its ability to modify brain activity for 20 minutes after just 40 seconds of stimulation, possibly reducing the duration of treatment. However, the precise mechanisms behind the rapid effects of TBS are not yet fully understood, requiring additional research through animal studies. Previous research on the auditory cortex (AC), essential for processing sound, has been relatively scarce. Additionally, most of these studies use large coils designed for humans, which can activate the entire brain of rodents, thus obscuring the effects on specific brain regions. The goal of this study was to determine whether TBS can modulate mouse AC

activity. To achieve this, we created a millimeter-sized prototype coil with a permalloy core, designed to target stimulation to specific areas of the cerebral cortex. We numerically estimated the appropriate stimulation intensity that can stimulate the AC, which resulted in a peak-to-peak voltage of more than 40 V. After anesthetizing the mice, a 16-channel silicon probe was inserted into the exposed AC. To evaluate the modulatory effect of TBS on the AC, we applied three different types of TBS to the AC: (i) continuous TBS (cTBS, TBS continuously delivered for 40 seconds), which is generally known for its inhibitory effects; (ii) intermittent TBS (iTBS, 2-second TBS delivered every 10 seconds for a total of 200 seconds), which typically has facilitatory effects; and (iii) a sham condition with no voltage input (0 V) to the coil. We measured TMS-evoked activities (TEA) in the AC from 5 minutes before to 30 minutes after applying TBS, at 5-minute intervals. The results showed an increase in both local field potential (LFP) amplitudes and spike waveform amplitudes following iTBS. Conversely, a decrease was observed in LFP amplitudes and the number of spikes following cTBS. Only the increase in spike waveform amplitude following iTBS occurred relatively late (after 15 minutes), possibly relating to the decrease in calcium-binding protein regulation reported in previous studies. Overall, our study confirms that our TBS protocols can effectively modulate activity in the mouse AC. Further research into the specific auditory features affected by TBS, such as frequency tuning and tonotopy, is essential for translating these findings into clinical practice for treating hearing disorders.

Disclosures: T. Yoshikawa: 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.; Japan Society for the Promotion of Science. **T. Tateno:** 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.; Japan Society for the Promotion of Science, Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering, Suzuken Memorial Foundation.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.02/G10

Topic: I.08. Methods to Modulate Neural Activity

Support: BRAIN Initiative NINDS R01NS120850

Title: Propagation of electrically evoked neural activity in mice

Authors: *J. L. HICKMAN[1], D. J. DENMAN[2];
[1]Univ. of Colorado Anschutz Med. Campus, Aurora, CO; [2]Univ. of Colorado Anschutz, Aurora, CO

Abstract: Electrical brain stimulation (EBS) is a widely used clinical and basic science tool, but how EBS modulates the surrounding the neural tissue and spiking activity of nearby neurons remains poorly characterized in vivo. To address this, we implanted three Neuropixels orthogonal to a stimulating electrode through which EBS was applied in the mouse primary visual cortex. We registered the recording and stimulating electrodes to the Common Coordinate Framework to evaluate spatial properties of EBS (e.g, distance from stimulation and anatomical region). This allows us to compare the extracellular potential and the resulting modulation of single neurons in a volume surrounding the stimulation site to theoretical predictions. Increasing amplitude of stimulation increased the volume of the evoked potential symmetrically from the stimulation source. However, contrary to models that suggest bipolar stimulation spatially constrains the induced electric field, polarity did not change the volume or symmetry of the evoked potential. We found that probability of single unit spiking response within 3ms of stimulation increased with amplitude and decreased with distance. Notably, the probability was far below 100% for the closest single neurons, within a few hundred microns. Cell electrophysical properties including waveform shape, unit amplitude, and inter-spike interval distribution all had a small effect on direct response probability. The spatial response characteristics of the direct single-unit response correlate with that of the electrically evoked potential. Finally, we explored the indirect, circuit-level response to electrical brain stimulation. We found a robust temporal sequence of early excitation (0-15ms), inhibition (15-150ms), and rebound excitation (150-300ms) throughout cortex, extending beyond the spatial extent of the evoked potential and direct single-unit responses. However, this circuit-level response did not propagate subcortically, even when evoked potentials extended subcortically. The specific magnitude and duration of each temporal epoch varied with stimulation parameters. These experiments provide in vivo characterizations of the neural response to EBS to directly test hypotheses generated from modeling and inform both clinical and research applications of EBS such as deep brain stimulation and sensory prosthetics.

Disclosures: J.L. Hickman: None. **D.J. Denman:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.03/G11

Topic: I.08. Methods to Modulate Neural Activity

Support: 5I01RX001640-09

Title: The importance of post-inhibitory rebound during neuromodulation of motor cortex dynamics with thalamic stimulation

Authors: *K. KIM[1], G. P. KRISHNAN[2], M. V. BAZHENOV[3], K. GANGULY[4];
[1]UCSF, San Francisco, CA; [2]Georgia Inst. of Technol., Atlanta, GA; [3]Dept. of Med., UCSD, La Jolla, CA; [4]Neurol., UCSF, San Francisco, CA

Abstract: Movement-related low-frequency cortical dynamics (~1-7 Hz) in local field potential (LFP) and spiking activity is present during the preparation and generation of tasks. Such low-frequency activity is closely associated with patterns of task-related population co-firing. Manipulation of cortical dynamics by direct electrical current stimulation (DCS) in the motor cortex is known to improve motor task performance during stroke recovery. However, there is a translational challenge of using current forms of DCS since it is substantially greater than current FDA limits for charge density. The motor thalamus (Mthal), which is a major pre-synaptic input to the motor cortex, may be a viable alternative to modulate large-scale networks. We tested Mthal electrical current stimulation using bursts of biphasic pulses to induce motor cortical activity while also modulating the overall frequency of stimulation in male rats. Mthal stimulation drove upstate in primary (M1) and secondary motor cortex (M2) synchronously. Importantly, there was a post-stimulation inhibition (200-400ms post stimulation) followed by rebound spike activity in M1 and M2. We then systematically varied the stimulation burst frequency from 1-8 Hz. Compared to smaller than 4Hz stimulation, greater than 4Hz stimulation revealed less cells directly entrained by the stimulation. Interestingly, 7-8Hz stimulation showed marked depression during stimulation, in both the LFP and spiking activity. To investigate the underlying mechanisms causing frequency dependent modulation by Mthal burst stimulation, we tested the effects of stimulation in a computational model of thalamocortical networks. The computational model implemented different synaptic connections (i.e., AMPA, MNDA and GABA) in various type of cells (i.e., pyramidal cells, inhibitory cells in cortex, thalamocortical, and thalamic reticular nucleus). In the model, Mthal burst stimulation also resulted in feed-forward inhibition in cortical area. The model revealed that cortical rebound was triggered by rebound spike activity of thalamocortical cells after burst firing of the thalamic reticular nucleus. Together, these results suggest that lower than 4Hz Mthal stimulation can be effective in inducing large-scale cortical low-frequency. These results further suggest that optimizing Mthal stimulation parameters can allow targeted improvements of motor function after stroke.

Disclosures: K. Kim: A. Employment/Salary (full or part-time):; UCSF. **G.P. Krishnan:** None. **M.V. Bazhenov:** None. **K. Ganguly:** A. Employment/Salary (full or part-time):; UCSF.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.04/G12

Topic: E.05. Brain-Machine Interface

Support: NIH K12HD073945
Morton Cure Paralysis Fund

Title: Muscle responses to multi-site optogenetic peripheral motor nerve stimulation in transgenic mice and virus-injected rats

Authors: *E. M. MORAVEC[1], J. J. WILLIAMS[1,2];
[1]Biomed. Engin., Marquette Univ. and Med. Col. of Wisconsin, Milwaukee, WI; [2]Neurosurgery, Medical College of Wisconsin, Milwaukee, WI

Abstract: Optogenetic stimulation of peripheral motor nerves offers several attractive properties for stimulation of muscles paralyzed by conditions such as spinal cord injury. Previous studies have suggested that optogenetic stimulation provides a more physiologic motor unit recruitment order and reduced fatigue compared to traditional electrical stimulation approaches. However, the relatively slow channel kinetics of standard opsins such as channel-rhodopsin2 (ChR2) limit the maximum effective stimulation frequency that can be used, and this value is generally below frequencies used to produce fused contractions with electrical stimulation. In this study, we sought to increase the effective stimulation frequency possible with optogenetic stimulation using spatial and temporal patterning. We first conducted experiments in Thy1-ChR2-eYFPmice, which express ChR2 in peripheral nerves throughout the body. For each animal, we surgically exposed the left peroneal nerve and placed a pair of electrodes in the left tibialis anterior muscle to record electromyograms (EMG). Spatially patterned optical stimulation was delivered to the nerve surface via a digital mirror device (DMD) coupled to a 463 nm laser. The output of the DMD was focused through a microscope objective onto the exposed nerve such that light was limited to a defined area. When two-second optical stimulation trains were applied to a single site along the nerve, EMG responses decayed quickly for stimulation frequencies above 20 Hz. We then defined multiple stimulation sites with equal area. Optical stimulation pulses were switched sequentially between sites such that each site was only stimulated at a fraction of the total frequency. EMG response magnitudes remained higher throughout the optical stimulation train with multi-site stimulation compared to a single site. Muscle responses to multi-site optical stimulation also decayed at a slower rate compared to stimulation of a single site with a larger area, though the overall magnitudes of the initial responses were smaller. Finally, we performed similar experiments in rats injected with a viral vector to induce ChR2 expression in the peroneal nerve. Multi-site stimulation also allowed for more effective stimulation at higher frequencies in these animals, suggesting that this approach will extend beyond transgenic animals with close to ideal opsin expression. Overall, these results demonstrate that multi-site alternating stimulation can improve high frequency performance during optogenetic stimulation and may enable more energy efficient stimulation by reducing the light needed to maintain muscle responses.

Disclosures: E.M. Moravec: None. **J.J. Williams:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.05/G13

Topic: E.05. Brain-Machine Interface

Support: Morton Cure Paralysis Fund
Medical College of Wisconsin Research Affairs Committee Pilot Award

Title: Optimizing viral optogenetic expression in axons for peripheral motor nerve applications

Authors: J. MURRAY[1], E. MORAVEC[1], *J. WILLIAMS[1,2];
[1]Joint Dept. of Biomed. Engin., Marquette Univ. and Med. Col. of Wisconsin, Milwaukee, WI;
[2]Dept. of Neurosurg., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Optogenetic stimulation has emerged as a promising technique for controlling peripheral nerve activity with light, offering advantages over traditional methods like electrical stimulation. Typical approaches involve injection of a viral vector to express light-sensitive opsin proteins into target nervous tissue, rendering them sensitive to light. For brain applications, optical stimulation is targeted to brain regions containing neuronal cell bodies of interest, which is also where opsin expression is typically highest. However, for applications targeting peripheral nerves (e.g. reanimation of paralyzed muscle activity using optical stimulation of motor nerves), opsins need to be expressed along axons in the periphery (as opposed to cell bodies in the spinal cord) to facilitate effective optical stimulation. To optimize vectors for such applications, this study aimed to investigate the utility of Neuritin (NRN1) in trafficking virally expressed opsins to peripheral nerve axons. NRN1 has previously been used as a viral transcriptional element to target fluorescent protein expression to axons for the purposes of tracing brain region connections. For this project, we examined whether a similar approach could be used to target viral opsin expression to peripheral motor nerves after intramuscular injection to improve their sensitivity to optical stimulation. To test this hypothesis, we injected an adeno-associated virus (AAV) vector with and without the NRN1 transcription element into the tibialis anterior muscle of rats in order to express the opsin, ChR2, along the peroneal nerve. To assess and compare functional optical sensitivity of targeted nerves, electromyography, video, and force measurements were collected weekly in response to transdermal optical nerve stimulation. At the end of the viral incubation period, histological analyses of fluorescent protein markers in targeted nerve and spinal cord samples were used to compare the quantity of transduced axons and the magnitude of peripheral opsin expression between vectors with and without NRN1. The results of these studies suggest that inclusion of NRN1 in AAV vectors intended for peripheral nerve expression increases the magnitude of opsin expression in peripheral nerve axons, thereby improving the nerve's functional sensitivity to optical stimulation. While we target these vectors to intramuscular injections for potential motor rehabilitation applications, this approach may be beneficial to a wide variety of gene therapy applications targeting modulation of peripheral nerve activity.

Disclosures: **J. Murray:** None. **E. Moravec:** None. **J. Williams:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.06/G14

Topic: I.08. Methods to Modulate Neural Activity

Title: Minimally-invasive electric stimulation techniques to target hippocampal theta in the urethane-anesthetized rat

Authors: *B. TESSLER[1], S. E. FOX[2];
[1]SUNY - Downstate Med. Ctr., Brooklyn, NY; [2]Dept Physiol & Pharmacol, State Univ. of New York Downstate Med. Ctr., Brooklyn, NY

Abstract: Electrical brain stimulation shows significant potential for studying normal and treating abnormal brain function, owing to the electrical nature of the brain. Non-invasive techniques, while attractive due to their affordability, ease of use, and low-risk nature, have limited effectiveness and mechanisms that are not well understood. Moreover, their ability to target deep brain regions is restricted, often affecting only surface areas. A novel technique, Temporal Interference (TI), has emerged as a promising method for reaching deeper targets. In this study, we used a virtual rat head model to optimize the locations for skull-mounted electrodes to stimulate the hippocampus. The hippocampus is a deep brain region that spontaneously generates theta, which is the brain's largest amplitude rhythm, associated with learning, memory, and has possible antiepileptic effects. We employed a range of stimulation techniques and observed their effects on brain rhythms. We used a novel stimulus artifact removal technique, Independent Component Analysis (ICA), to increase the certainty of the results. Our results indicated that all stimulation methods, in a stimulus intensity-dependent manner, increased the likelihood of spontaneous theta, as well as the frequency and power of theta at the onset of the stimulus, which persisted after the stimulus. TI and amplitude-modulated (AM) stimulation generated phase-locked theta to the wave envelope of the stimulation. We also found the magnitude of the effect was dependent on the pre-stimulus power of theta, indicating a dependency on brain state. This study is significant in advancing our understanding of electrical stimulation techniques for deep brain modulation, potentially leading to safe, low-cost, non-invasive treatments or experimental tools that can target previously inaccessible brain structures.

Disclosures: B. Tessler: A. Employment/Salary (full or part-time):; SUNY - Downstate Medical Center. **S.E. Fox:** A. Employment/Salary (full or part-time):; SUNY - Downstate Medical Center.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.07/G15

Topic: C.03. Parkinson’s Disease

Support: Japan Agency for Medical Research and Development (JP18dm0207070s0001, JP18dm0307003h0002, JP24wm0625001)
Japan Society for Promotion of Science KAKENHI (23H00414) 24K18241

Title: In-vivo brainstem volumetry in iRBD underpinned by a high-resolution ex-vivo MRI atlas

Authors: *M. HIROSE[1,2], K. YOSHINAGA[3], Y. MORI[3], N. WAKASUGI[4], H. IMAI[5], Y. TAKAHASHI[6], R. TAKAHASHI[7], T. HANAKAWA[3];
[1]Kyoto Univ. Grad. Sch. of Med., Kyoto, Kyoto, Japan; [2]Dept. of Neurol., [3]Dept. of Integrated Neuroanatomy and Neuroimaging, Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; [4]Dept. of Neurol., Tokyo Metropolitan Neurolog. Hosp., Tokyo, Japan; [5]Grad. Sch. of Informatics, Kyoto Univ., Kyoto, Japan; [6]Dept. of Neurol., Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan; [7]Res. Admin. Ctr., Kyoto Univ., Kyoto, Japan

Abstract: Background: Isolated rapid eye movement (REM) sleep behavior disorder (iRBD) is recognized as prodromal symptom of α-synucleinopathies. Exploring the brainstem pathophysiology underlying iRBD, as inferred from animal studies, is challenging in humans due to limitations in accurate localization of the brainstem microstructures with conventional MRI. We aimed to clarify brainstem pathological changes in iRBD by combining a high-resolution *ex-vivo* MRI-based brainstem atlas with *in-vivo* voxel-based morphometry (VBM) analysis. Method: VBM analysis was performed with in-vivo 3T MRIs acquired from 98 iRBD patients and 97 healthy aged people to detect brainstem gray matter volume differences between groups. For precise localization of this change, we created a novel brainstem atlas compatible with the Montreal Neurological Institute (MNI) standard space using high-resolution (78.1-μm isovoxel) T1-weighted images from 11 ex-vivo gadolinium-immersed postmortem human brainstems scanned with a 7-T scanner. ROIs of Brainstem nuclei and reticular formations were manually delineated and normalized to the MNI space in each ex-vivo image. Normalized ROIs were averaged among all specimens to construct a probabilistic atlas. Following MRI acquisition, the brainstems were paraffin-embedded, sliced, and stained with Kluver-Barrera (K-B) or immunohistochemistry for histological validation, enabling 2D-2D comparisons between MRI and histology. The ex-vivo atlas was then applied to the in-vivo VBM result to label the regions showing significant volume reductions in iRBD patients. Results: The VBM analysis revealed volume reductions in the midbrain-pontine tegmentum in iRBD patients compared to healthy aged. The ex-vivo study-based atlas focused on this region, defining 35 ROIs in the midbrain and upper pons. The combination of K-B staining and immunohistochemistry allowed for the validation of these ROIs. Applying the atlas to the in-vivo data allowed for a more detailed analysis of the affected structures, confirming significant volume reductions in the periaqueductal gray, dorsal raphe nucleus, left pontine tegmentum, and left laterodorsal tegmental nucleus in iRBD patients. Conclusion: By combining in-vivo MRI and an ex-vivo MRI-based brainstem atlas, our study demonstrates structural brainstem abnormalities in iRBD. These findings suggest neurodegeneration in key areas responsible for REM sleep regulation, offering potential biomarkers for iRBD and α-synucleinopathies.This study presents a novel approach to the neuroimaging studies, enhancing our understanding of iRBD and aiding in early diagnostic strategies of synucleinopathies.

Disclosures: M. Hirose: None. **K. Yoshinaga:** None. **Y. Mori:** None. **N. Wakasugi:** None. **H. Imai:** None. **Y. Takahashi:** None. **R. Takahashi:** 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.; Sumitomo Pharma Co., Ltd., Eisai Co., Ltd., Kyowa Kirin Co., Ltd.. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g.,

speakers' bureaus); Sumitomo Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Eisai Co., Ltd., Ono Pharmaceutical Co., Ltd.. F. Consulting Fees (e.g., advisory boards); Eisai, Co., Ltd., Sunwels, Co., Ltd.. **T. Hanakawa:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.08/G16

Topic: C.03. Parkinson's Disease

Support: NIH Grant 1ZIAEY000415

Title: Inactivation of the lower dorsal midbrain triggers involuntary saccadic intrusions and disrupts voluntary goal-directed eye movements

Authors: *H. LEE[1], O. HIKOSAKA[2];
[1]Natl. Eye Inst., Bethesda, MD; [2]Lab. Sensorimotor Res., Natl. Eye Inst., Bethesda, MD

Abstract: For a proper execution of voluntary action, it is pivotal to control various involuntary movements. The interruption of uncontrolled movements is particularly evident in Parkinson's patients, who exhibit not only difficulties in initiating intended movements or bradykinesia but also accompany it with unwanted involuntary movements such as tremors and dyskinesia. Eye movements serve as important indicators of voluntary goal-directed behavior. In the goal-directed behavior, the superior colliculus located at the roof of the dorsal midbrain is crucial to signal reward information of targets to the abducens nerve and burst premotor neurons to guide horizontal saccadic eye movements. Meanwhile, in the lower part of the dorsal midbrain, the central mesencephalic reticular formation and periaqueductal gray contain neurons that project to the omnipause neurons in the nucleus raphe interpositus, which control gaze fixation. Additionally, around the border of the periaqueductal gray, ocular-related nuclei such as the oculomotor, trochlear, Edinger-Westphal, Darkschewitz, and interstitial nucleus of Cajal are distributed and coordinate various components of eye movements. Particularly, the lower part of the dorsal midbrain is reported to show the most significant reduction of dopamine release in advanced Parkinson's disease patients, alongside a deficiency of substantia nigra pars compacta dopamine neurons in the ventral midbrain. Through non-human primate research, we observed that inactivation of the lower part of the dorsal midbrain by injecting the GABAergic agonist muscimol led to the occurrence of frequent unwanted saccadic intrusions in monkeys, particularly during the inter-trial interval of visually guided tasks that monkeys were performing to obtain a reward. These unwanted eye movements during the inter-trial interval disrupted voluntary goal-directed behavior during task trials by causing slow saccadic reactions toward visual cues and drift interfering with gaze holding on the eccentric gaze position at the end gaze. To understand the mechanisms underlying the dysfunction of inhibitory control in involuntary behaviors, we investigated the electrophysiological properties of diverse neuronal subpopulations in the periaqueductal gray surrounding areas.

Disclosures: **H. Lee:** None. **O. Hikosaka:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

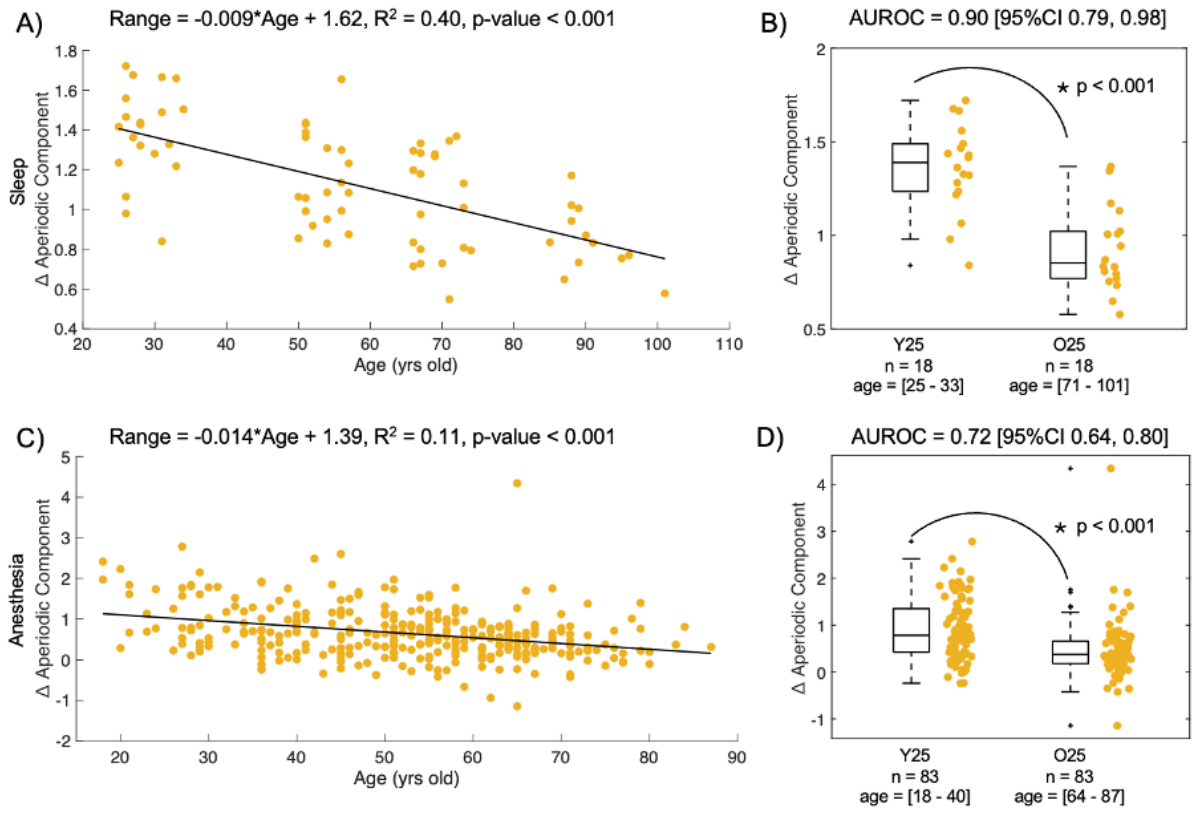
Program #/Poster #: PSTR028.09/Web Only

Topic: I.08. Methods to Modulate Neural Activity

Title: Age decreases the dynamic range of EEG changes between vigilant states

Authors: *C. TROYAS[1], P. S. GARCIA[2], G. SCHNEIDER[3], M. KREUZER[4];
[1]Tech. Univ. of Munich, München, Germany; [2]Anesthesiol., Columbia, New York, NY; [3]Anesthesiol. and Intensive Care, Tech. Univ. Munich, Muenchen, Germany; [4]Anesthesiol. and Intensive Care, Tech. Univ. of Munich, Muenchen, Germany

Abstract: Background: Intraoperative electroencephalographic (EEG) monitoring is used to individualize the dosing of analgesic and hypnotic anesthetics. Age-related changes in neurophysiology are known to influence EEG signals. We measured EEG spectral slope changes in different vigilance states with age. The dynamic range of spectral slope observed in EEGs from distinct sleep and anesthesia states provides insight into age-related neurophysiologic changes. **Methods**: We analyzed 135 publicly available sleep EEGs from 72 subjects 25-101 years old[1]. For each subject, we extracted the N1 (light sleep) and N3 (deep sleep) EEG, calculated power spectra, and applied the "fitting oscillations & one over f" algorithm to obtain the EEG's aperiodic component (spectral slope). We defined the dynamic range as the difference between the N3 and N1 spectral slope. We performed a similar analysis using 324 EEGs (18-87 years old) during anesthesia maintenance and emergence. The dynamic range was the difference between maintenance and emergence. **Results/Discussion**: The spectral slope's range (Δ) decreased linearly with age for sleep (Δ=-0.009*age+1.62; R^2=0.40) and anesthesia (Δ=-0.014*age+1.39; R^2=0.11). The youngest subjects (1st quartile, Y25) showed a significantly higher dynamic range than the oldest quartile (O25). Age had a "strong" effect on the range (median[IQR] Sleep Y25: 1.36[1.23, 1.49], O25: 0.92[0.77, 1.02], p<0.001, AUC:0.90[0.79, 0.98]; Anesthesia Y25: 0.92[0.42, 1.35], O25: 0.47[0.18, 0.66], p<0.001, AUC:0.72[0.64, 0.80]). Thus, the young brain expressed a larger dynamic range between the more "awake" (N1/maintenance) and "sleepier" (N3/emergence) state than the old brain. **Conclusion**: We found a reduced dynamic range between different vigilant stages in older subjects during both sleep and anesthesia, reflecting an age-related change in brain dynamics. These results have the potential to help individualize the administration of anesthetic agents in patients across the age spectrum and identify patients at risk for postoperative cognitive decline. **Ref:** PMID 11008419



Disclosures: C. Troyas: None. **P.S. Garcia:** A. Employment/Salary (full or part-time):; Department of Anesthesiology, Columbia University Irving Medical Center. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); The research effort of Dr. Paul S. García is supported in part by the James S. McDonnell Foundation (St. Louis, Missouri), grant No. 220023046.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Drs. Kreuzer and Garcia are named as inventors for a patent recently filed on a method for intraoperative EEG monitoring that accounts for spectral and entropic features of age (System, method and com. **G. Schneider:** A. Employment/Salary (full or part-time):; Department of Anesthesiology and Intensive Care Medicine, Technical University of Munich, School of Medicine, Munich, Germany. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Drs Schneider, García, and Kreuzer are named as inventors for a patent filed on a novel method for intraoperative EEG monitoring (System, method and computer-accessible medium for anesthesia monitorin. **M. Kreuzer:** A. Employment/Salary (full or part-time):; Department of Anesthesiology and Intensive Care Medicine, Technical University of Munich, School of Medicine, Munich, Germany. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Dr. Kreuzer received financial support from Medtronic to hold the SBI EEG Bootcamp.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Drs. Kreuzer and Garcia are named as inventors for a patent recently filed on a method for intraoperative EEG monitoring that accounts for spectral and entropic features of age (System, method and com.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.10/Web Only

Topic: I.08. Methods to Modulate Neural Activity

Title: Nonlinear connectivity measures demonstrate different functional brain network features in graph theory analysis: an investigation by source localized eeg

Authors: *Y. SHADMANESH[1], S. KHAZEI[1], A. GHADERI[2];
[1]Isfahan Univ., isfahan, Iran, Islamic Republic of; [2]York Univ., Toronto, ON, Canada

Abstract: While the core architecture of brain networks remains remarkably consistent across healthy individuals, different connectivity measures may reveal various architectures for these networks. Brain regions don't operate in isolation; the strength and efficiency of their connections influence information flow linearly or non-linearly. In this study, we applied graph theory analysis to explore changes in functional brain networks in healthy individuals when we use different functional connectivity measures to build these networks. To this aim we compared topological features of these networks characterized by three different lagged linear or non-linear connectivity measures. Thirty-six individuals participated in this study, and resting state EEG in eye closed condition was recorded. Subsequently, we applied the sLORETA source localization algorithm to find current densities of EEG sources in 84 cortical Brodmann areas. Then, functional brain networks were derived from calculation of three measurements i.e., lagged nonlinear connectivity, lagged coherence and lag phase synchronization. As a measure of functional segregation, the clustering coefficient was calculated for each participant and functional integration in the brain was measured using global efficiency In seven distinct frequency bands (delta, theta, alpha, beta1, beta2, beta3 and gamma), and the results were compared among three groups by performing t-tests. Results showed that networks constructed by lagged non-linear connectivity and lagged phase synchronization were mostly similar in different frequency bands (in term of topological features). On the other hand, lagged non-linear connectivity and lagged coherence showed the most different topological features. These results suggest that selecting the connectivity measures to construct functional brain networks significantly changes the result. Particularly, non-linear connectivity measures may reveal alternative properties of functional brain networks in healthy individuals.

Disclosures: **Y. shadmanesh:** None. **S. Khazei:** None. **A. Ghaderi:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.11/G18

Topic: E.05. Brain-Machine Interface

Support: NIH F99NS130828
NIH R01NS119395
NIH P51OD010425

Title: Optogenetic homeostatic priming of Hebbian-informed stimulation facilitates connectivity change in macaque posterior parietal cortex

Authors: *K. KHATEEB[1], J. ZHOU[2], F. SCHWOCK[1], T. BELLOIR[1], A. YAZDAN-SHAHMORAD[3];
[1]Univ. of Washington, Seattle, WA; [2]Bioengineering, Univ. of Washington, Seattle, WA; [3]Bioengineering and Electrical Engin., Univ. of Washington, Seattle, WA

Abstract: The connectivity between neurons in the brain are known to constantly change during learning and following disease and injury through inherent plasticity mechanisms. To enhance recovery from functions lost to neural damage, such as sensorimotor deficits, clinical interventions often leverage neuromodulation techniques in attempt to direct these plasticity mechanisms. Commonly, Hebbian plasticity-based approaches are utilized, where the simultaneous co-activation of neurons enhances their connectivity (long-term potentiation, LTP). While Hebbian-informed paired stimulation has been successfully demonstrated in vitro, this has not been the case with in vivo studies. Often overlooked in these approaches are homeostatic plasticity mechanisms that work to maintain consistent neuronal activity levels. In particular, it is hypothesized through homeostatic metaplasticity mechanisms that in response to reduced neuronal activity levels, the threshold for LTP induction is also reduced. Here, we hypothesize that a stimulation-based approach integrating both Hebbian and homeostatic metaplasticity mechanisms may result in greater functional connectivity changes in comparison with Hebbian-based approaches alone.We applied optogenetic homeostatic priming followed by Hebbian-informed paired electrical stimulation in the posterior parietal cortex of two adult male macaques. Both animals were previously implanted with a chronic optogenetic neural interface that allows for Jaws-mediated neuronal inhibition and electrocorticographic (ECoG) recording and stimulation of neural activity. Our experimental protocol included four consecutive phases: baseline activity recording, optogenetic homeostatic priming, Hebbian-informed paired electrical stimulation, and post-stimulation recording.We measured changes in signal coherence and Granger causality across the ECoG array to assess functional connectivity changes. We observed that our integrated approach significantly increased functional connectivity between stimulated areas and throughout the network compared to sham controls. The results of this study demonstrate that the integration of multiple mechanisms of plasticity in stimulation-based approaches can yield heightened neuronal connectivity and may better promote functional recovery following neural injury or disease compared to other approaches.

Disclosures: K. Khateeb: None. **J. Zhou:** None. **F. Schwock:** None. **T. Belloir:** None. **A. Yazdan-Shahmorad:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.12/G19

Topic: E.05. Brain-Machine Interface

Support: CIHR PJT-183769-2022
Brain Canada Foundation - WBHI
Brain Canada Foundation - Future Leaders 2019

Title: Effect of VTA on M1 Neural Activity

Authors: *A. M. MIAO[1], V. SAVARD[2], M. DEMERS[3], C. ETHIER[4];
[1]Laval Univ., Quebec City, QC, Canada; [2]Laval Univ., quebec, QC, Canada; [3]CERVO, Quebec, QC, Canada; [4]Psychiatrie et Neurosciences, Univ. Laval - CERVO, Quebec, QC, Canada

Abstract: The primary motor cortex (M1) is responsible for fine motor execution and motor learning. Learning is known to be associated with neuronal plasticity. Dopaminergic signaling in M1 is necessary for successful motor learning and is thought to modulate M1 neuronal plasticity. Dopaminergic axons in M1 from the ventral tegmental area (VTA), which also send long-range GABAergic and glutamatergic projections to M1. The functional role of this complex VTA-M1 pathway remains poorly understood. Our objective here is to characterize the influence of the VTA-M1 pathway on M1 neuronal activity under different behavioral conditions. To this end, we used intracortical multielectrode arrays in rats to record M1 responses to VTA optogenetic stimulation. Using different viral vectors in TH::Cre rats, we were able to target VTA dopamine neurons, either specifically or along with glutamatergic neurons. We assessed the immediate impact of their activation on the activity of individual M1 neurons in different behavioral conditions: under anesthesia, during free behavior, or during motor learning. We found a clear modulation of M1 activity during and after VTA stimulation. This effect of VTA stimulation on individual M1 neurons was diverse and varied during different behavioral conditions. Neuronal population responses were analyzed using dimensionality reduction. A clear trajectory representing neural population changes was observed. These results suggest that VTA-M1 projections could reshape neuronal activity in M1 and may facilitate fine motor learning and neuronal plasticity.

Disclosures: **A.M. Miao:** None. **V. Savard:** None. **M. Demers:** A. Employment/Salary (full or part-time):; CERVO. **C. Ethier:** A. Employment/Salary (full or part-time):; Laval University.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.13/G20

Topic: E.05. Brain-Machine Interface

Support: NIH R01 EB027584
ANR-18-NEUC-0002-02

Title: Neuromodulation of Nerve Fiber Activation via Intrafascicular Stimulation: Effects of Non-Rectangular Waveform Shapes

Authors: *A. ORTEGA SANABRIA[1], L. REGNACQ[2], J. ASBEE[1], A. K. THOTA[1], J. J. ABBAS[1], L. M. MCPHERSON[3], R. JUNG[1];
[1]Inst. for Integrative and Innovative Res., Univ. of Arkansas, Fayetteville, AR; [2]Univ. Bordeaux, Bordeaux INP, IMS CNRS UMR 5218, Paris, France; [3]Physical Therapy, Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Neuromodulation of peripheral nerves is used as bioelectronic medicine to treat diseases. Electrical stimulation is applied to a peripheral nerve to exert control over biological processes. However, higher selectivity is often necessary to reduce off-target activation and to activate the necessary subpopulation of fibers to get the desired outcome. Selectivity depends on the neural interface, electrode type and stimulation parameters including pulse waveform shape, frequency, and other factors. Currently, most applications of electrical stimulation utilize biphasic symmetrical pulses. In this study, the effects of waveform shape on nerve fiber activation for neurostimulation was investigated using multiple longitudinal intrafascicular electrodes (LIFEs) implanted in the sciatic nerve of rats. The non-rectangular waveform shapes studied were sinusoidal, triangular, linear incline and linear decline. Selectivity of nerve fiber recruitment for motor fiber recruitment was assessed using a 32 channel High-Density epymisial electromyogram (HD-eEMG) grid that provided spatiotemporal information about motor fiber activation (M-waves) of the innervated gastrocnemius lateralis (GL) muscle. Experiments were conducted in anesthetized adult male Sprague-Dawley rats (n=6) and 2 to 3 LIFEs were implanted in the tibial fascicle of the sciatic nerve. Pulse amplitude was modulated from threshold up to 1.5xthreshold at a pulse width at chronaxie based on the strength-duration curves for each electrode and each waveform shape. For each waveform shape, monopolar biphasic asymmetrical pulses (ratio of the anodic to cathodic phase was 12) were delivered at 10Hz for 5 seconds using a custom neurostimulator. Root Mean Square (RMS) of the M-waves for each channel were used to assess spatiotemporal spread of muscle twitch. The results showed that the type of pulse, commonly used biphasic rectangular pulses vs different waveform shapes, has an effect on the RMS values of the M-waves ($p < .001$). Additionally, when analyzing the effects of each of these waveform shapes, the results showed that Sine $p < .001$, Triangular $p < .001$, Linear Incline $p < .001$ and Linear Decline $p < .01$ shapes reduce the RMS values across the grid. The effect size of these results is small. This suggests that the fibers are activated differently depending on the waveform shape used. Further analysis needs to be performed but these findings could provide an insight into the use of different waveform shapes to target the specific fibers and enhance nerve fiber selectivity of neurostimulation using LIFEs.

Disclosures: A. Ortega Sanabria: None. **L. Regnacq:** None. **J. Asbee:** None. **A.K. Thota:** None. **J.J. Abbas:** None. **L.M. McPherson:** None. **R. Jung:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.14/G21

Topic: I.08. Methods to Modulate Neural Activity

Title: Neurostimulation for the quantification and classification of human single-neurons

Authors: *E. H. SMITH[1], E. M. MERRICKS[2], T. S. DAVIS[1], B. KUNDU[3], S. RAHIMPOUR[4], B. SHOFTY[5], J. D. ROLSTON[6], C. A. SCHEVON[7], R. L. COWAN[5];
[1]Univ. of Utah, Salt Lake City, UT; [2]Neurol., Columbia Univ. Med. Ctr., New York, NY; [3]Neurosurg., Univ. of Missouri, Columbia, MO; [4]Duke Univ. Hlth. Syst., Durham, NC; [5]Neurosurg., Univ. of Utah, Salt Lake City, UT; [6]Neurosurg., Brigham and Women's Hosp., Boston, MA; [7]Columbia Univ. Irving Med. Ctr., New York, NY

Abstract: Little is known about how deep brain stimulation affects local neuronal firing. Here, we capitalize on the ability to record single-unit activity in response to single, biphasic pulses of direct electrical stimulation of the human brain. We quantify several features of neuronal responses to stimulation at varying distances from the stimulation electrode, in both gray and white matter, and of putative principal cells (PCs) and interneurons (INs). We stimulated each pre-selected macroelectrode ~10 times at 3mA (pulse-width 0.2s) every 1s in monopolar configuration. Each stimulation session lasted around 40 minutes, during which we recorded intracranial single-unit activity from Behnke-Fried microelectrodes in 28 subjects who had undergone invasive surgery for drug-resistant epilepsy (DRE). Additionally, we clustered units as PCs or INs, based on action potential waveform features to understand responses in these cell types. Out of 203 recorded units, 90 (44.34%) were modulated by stimulation, 57% of which showed suppressed firing and 43% of which showed increased firing, in response to stimulation. Responsive units had a mean baseline firing rate of 16.96 ± 12.42 Hz, mean suppression amplitude of 18.33 ± 14.24 Hz, and mean suppression latency of 0.37 ± 0.40s. We observed neuronal characteristic differences based on the euclidean distance of the unit from the stimulation site. Units within 8.5 mm of the stimulation site were classified as *near* units. All other units were classified as *far*. We show several significant differences between *far* and *near* stimulation, including decreased time to peak suppression from stimulation in gray matter. Finally, we observed unique response characteristics of cell types (i.e., significantly faster suppression latencies for INs). Overall, this in-depth analysis of unit response to stimulation allows us to disentangle the neuronal characteristics, stimulation parameters, and connectivity of white and gray matter in the human brain. These results not only answer open questions in the neuromodulation field but are also pertinent to the efficacy of treatments for neurological disorders, such as the localization of responsive neurostimulation for DRE.

Disclosures: E.H. Smith: None. **E.M. Merricks:** None. **T.S. Davis:** None. **B. Kundu:** None. **S. Rahimpour:** None. **B. Shofty:** None. **J.D. Rolston:** None. **C.A. Schevon:** None. **R.L. Cowan:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.15/G22

Topic: I.08. Methods to Modulate Neural Activity

Support: Schmidt Futures Foundation SF 857
National Human Genome Research Institute Grant 1RM1HG011543
National Science Foundation Grant 2134955

Title: Electrical stimulation for goal-oriented learning in cortical organoids

Authors: *A. ROBBINS[1], H. SCHWEIGER[2], S. HERNANDEZ[1], A. SPAETH[1], K. VOITIUK[1], T. VAN DER MOLEN[3], D. PARKS[1], G. KAURALA[1], T. SHARF[4], M. A. MOSTAJO RADJI[5], M. TEODORESCU[1], D. HAUSSLER[6];
[1]Univ. of California, Santa Cruz, Santa Cruz, CA; [2]Molecular, Cell, and Developmental Biol., Univ. of California, Santa Cruz, Bakersfield, CA; [3]Univ. of California, Santa Barbara, Goleta, CA; [4]Biomolecular Engin., Univ. of California, Santa Cruz, Santa Cruz, CA; [5]Genomics Inst., Univ. of California, Santa Cruz, Santa Cruz, CA; [6]Genomics Inst., UCSC, Santa Cruz, CA

Abstract: Recent electrophysiology advances have enabled high-density neuronal recordings and targeted electrical stimulation. Cortical organoids derived from induced pluripotent stem cells (iPSCs) have shown great promise as in-vitro lab-grown models of the brain, yet in the absence of external input, they are informationally isolated. In this paper, we embody mouse cortical organoids into a simulated dynamical task to evaluate learning through specifically designated training signals. We developed a closed-loop electrophysiology framework that enables task-specific benchmarking. First, we characterize the network by recording spontaneous activity to detect putative neural spatiotemporal footprints. We then utilize targeted neural stimulation to identify peri-stimulus time histograms (PSTH) and calculate causal connectivity. Next, we use this characterization of individual neural units to select a neural configuration involving input, output, and training neurons. Finally, we evaluate the network on the simulated inverted pendulum problem known as ‘cartpole’. Longitudinal experiments enabled by this framework illuminate how different methods of selecting training signals enable improvement on the tasks. We use rate-coding to encode/decode environmental information to/from the organoids. By holding constant the method of dynamically encoding and decoding information, we focus on the selection of the proper training signal from all possible paired pulses involving the training neurons. We found that for most organoids, training signals chosen by artificial reinforcement learning yield better performance on the task than randomly chosen training signals or the absence of a training signal. Certain organoids and neural configurations yield strong learners capable of rapid adaptation to the task. This work demonstrates, for the first time, goal-oriented learning in a brain organoid.

Disclosures: A. Robbins: None. **H. Schweiger:** None. **S. hernandez:** None. **A. Spaeth:** None. **K. Voitiuk:** None. **T. van der Molen:** None. **D. Parks:** None. **G. Kaurala:** None. **T. Sharf:** None. **M.A. Mostajo Radji:** None. **M. Teodorescu:** None. **D. Haussler:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.16/G23

Topic: I.08. Methods to Modulate Neural Activity

Title: Using transcranial magnetic stimulation to modulate shifts in attention

Authors: *A. ALEXANDERSEN[1], G. CSIFCSÁK[2], M. MITTNER[3];
[1]The Arctic Univ. of Norway, Tromsø, Norway; [2]Dept. of Psychology, Univ. of Tromsø, Tromsø, Norway; [3]Dept. of Psychology, Inst. For Psychology, Univ. of Tromsø, Tromso, Norway

Abstract: Mind wandering (MW) is a common mental phenomenon where attention shifts spontaneously from external tasks to internal trains of thought. Recent studies propose that non-invasive brain stimulation methods hold potential for influencing attentional shifts between on-task and MW states. Particularly, repetitive transcranial magnetic stimulation (rTMS) directed at the angular gyrus (AG), a crucial node in the default mode network (DMN) thought to be involved in initiating and sustaining MW content, has emerged as a promising approach for modulating MW. In particular, a recent study reported that inhibitory continuous theta-burst stimulation (cTBS) targeting the left AG reduced MW compared to sham stimulation, without influencing executive performance (Drevland et al., 2024). The present study is a preregistered direct replication, which also expanded the protocol by incorporating excitatory intermittent theta-burst stimulation (iTBS) targeting the same cortical area. Using a triple-blinded crossover design, healthy participants completed four blocks of the Finger-Tapping Random Sequence Generation Task across three sessions (with a minimum 7-day interval between sessions). Each session included three rounds of either real (cTBS or iTBS) or sham stimulation. We have successfully replicated the effect of cTBS in reducing MW propensity. Additionally, we also found evidence for increased frequency of MW reports following iTBS. Overall, our results provide evidence for the causal relationship between the left AG and shifts of attention during an executive task, highlighting the role of the DMN in the generation and maintenance of MW episodes. Furthermore, this study points at TBS as a potent tool for manipulating MW propensity in healthy adults, which may have clinical implications for non-invasively improving on-task focus in various psychiatric conditions.

Disclosures: A. Alexandersen: None. **G. Csifcsák:** None. **M. Mittner:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.17/G24

Topic: E.05. Brain-Machine Interface

Support: NIH R01: NS115707
NIH F31:NS125982

Title: Astrocyte Gq Activity Influences Neural Activity During Intracortical Microstimulation

Authors: *K. STIEGER, T. D. KOZAI;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Neural interfaces can generate artificial sensation by stimulating neurons through intracortical microstimulation (ICMS). Recent attention has turned to the role of astrocyte calcium activity and its impact on sensory processing. However, the precise influence of astrocyte calcium activity on neural activity during ICMS remains unclear. We hypothesize that increases in Gq-mediated astrocyte calcium activity plays a role in stabilizing or attenuating neural activity during prolonged trains of ICMS (30s). To test this hypothesis, we aimed to measure astrocyte or neuron calcium activity (GCaMP8m) during ICMS under two-photon (population-level) and mesoscale (network-level) imaging while modulating astrocyte Gq activity with chemogenetics or optogenetics. We previously demonstrated that activating a Gq-coupled DREADD (GFAP-HM3D(Gq)-mCherry) on astrocytes suppressed ICMS-induced astrocyte calcium activity, with the degree of suppression varying depending on the stimulation pattern (i.e. uniform vs bursting; 2-way ANOVA interaction two-photon: $p < 1e-4$; mesoscale $p<0.05$; N=3). Additionally, this suppression was associated with a significant increase in mesoscale neuronal calcium activity during stimulation (2-Way ANOVA, DREADD effect $p<0.05$, N=4). Next, to test if amplifying astrocyte calcium activity attenuates neural activity during ICMS, we combined ICMS with photostimulation of the Gq-coupled opsin, melanopsin, expressed on astrocytes. This photostimulation (471nm, 1mW, 1s, 10 Hz, 30ms pulse width) increased astrocyte calcium activity that peaked within 4.14 ± 1.15 s and was 1.3-7.9 times larger than astrocyte calcium activity elicited from ICMS alone (N=1, trials=3). Importantly, increasing Gq-mediated astrocyte calcium activity through photostimulation during ICMS quickly attenuated neural calcium activity. Specifically, neural calcium activity reduced by 27% and 19% between the 4 seconds before and 4 seconds after photostimulation for 10 Hz and 100 Hz ICMS, respectively. In comparison, ICMS alone resulted in an 24% increase for 10 Hz and a 9 % decrease in neural activity during the same period (N=1, trials=3). Together these data support the hypothesis that Gq-mediated astrocyte activity during ICMS may contribute to the stabilization or attenuation of neural activity. Overall this study enhances our understanding of the complex cellular dynamics during ICMS and underscores the pivotal role of astrocytes as modulators of stimulation-induced neural activity.

Disclosures: K. Stieger: None. **T.D. Kozai:** None.

Poster

PSTR028: Brain Machine Interfaces: Neurophysiology

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.18/G25

Topic: E.05. Brain-Machine Interface

Support: NIH Grant 5R01NS111518-04

Title: Hollow Tissue-Engineered Electronic Nerve Interfaces

Authors: *J. W. JUDY[1], B. W. SMADI[2], K. A. FLUKER JR.[1], A. LIM[2], K. J. OTTO[3]; [1]Nanoscience Inst. for Med. and Engin. Technol., Univ. of Florida, Gainesville, FL; [2]Biomed. Engin. Dept., Univ. of Florida, Gainesville, FL; [3]Biomed. Engin. Dept., Purdue Univ., West Lafayette, IN

Abstract: In the United States, more than 185,000 people experience limb amputation, which is a life-changing event with profound and long-lasting impact on the individual's quality of life. Although prosthetic limbs are often used to restore the function lost by amputees, the level of function restored is a function of a few important considerations: the prosthetic limb capability, the interface technology employed by the amputee to control the limb, and the patient's willingness to accept and/or adapt to the prosthesis. Despite the significant improvement in the functional capability of prosthetic limbs over the past 15 years, which includes state-of-the-art limbs that have more than 20 independent degrees of motional freedom and the ability to sense and deliver different forms of sensory information (e.g., force, pressure, shear, temperature, etc.) the capability of human-machine interfaces to control these advanced limbs has not improved nearly as much over the same time period. The inability of existing interfaces, specifically neural interfaces, to control advanced prosthetic limbs is hindering their translation and use by amputees. In our study, we build upon the innovative Tissue Engineered Electronic Nerve Interface (TEENI) technology, which utilizes multi-electrode arrays in hydrogel scaffolds, to introduce a more advanced and effective nerve regeneration approach. The hollow TEENI we developed expands on the original design, which was effective for neuronal recovery but had shortcomings in hydrogel degradation, leading to residue accumulation and potential immune responses. By introducing a hollow SIS structure, we aim to overcome these limitations, ensuring a smoother integration process and a more natural nerve healing, thereby enhancing the reconnection and functionality of nerves. This evolution marks a significant step forward in the application of TEENI technology in neural interfaces.

Disclosures: J.W. Judy: A. Employment/Salary (full or part-time):; University of Florida. 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.; 5R01NS111518-04. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Axogen Corporation. **B.W. Smadi:** A. Employment/Salary (full or part-time):; University of Florida. **K.A. Fluker Jr.:** A. Employment/Salary (full or part-time):; University of Florida. **A. Lim:** A. Employment/Salary (full or part-time):; University of Florida. **K.J. Otto:** A. Employment/Salary (full or part-time):; Purdue University.

Poster

PSTR029: Advances in Brain Computer Interfaces

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: /

Topic: E.05. Brain-Machine Interface

Support: NIH DP2-MH126378
NIH R01MH123770
NSF CRCNS IIS-2113271

Title: A nonlinear dynamical model for optimal control of neural states

Authors: *D. TYULMANKOV[1], E. BILGIN[2], E. ERTURK[2], M. M. SHANECHI[2];
[2]Electrical and Computer Engin., [1]USC, Los Angeles, CA

Abstract: Closed-loop regulation of neural activity can both help study causal interactions across brain networks and develop brain-computer interfaces for closed-loop neuromodulation in neurological and neuropsychiatric disorders. However, closed-loop control of neural states is hindered by the complexity of neural population dynamics and their response to external inputs. Thus far, closed-loop control methods have focused on simple approaches such as those based on linear models because developing controllers for nonlinear models can be challenging. However, linear models may not capture sufficient complexity for accurate control. Here, we develop a nonlinear encoding model of neural population activity that can describe neural dynamics in tractable form and thus allow for developing a closed-loop controller.
We validate our model and controller in a variety of simulated benchmark systems. In each case, our model successfully achieves its control objective of stabilizing the system at a desired target setpoint, and outperforms other baseline models. Finally, to explicitly demonstrate our model's utility as a brain-computer interface for restoring loss of function in neural systems, we design an in-silico experiment in which we use our method to restore the performance of a perturbed artificial recurrent neural network trained on a motor task. Overall, our method shows significant promise as a model-based controller for nonlinear systems, particularly well-suited for real-time control of neural dynamics.

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Poster

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Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.01/G26

Topic: E.05. Brain-Machine Interface

Support: BioInterNect PR23-PAS-P2

Title: Decoding pudendal intraneural signals for real-time bladder pressure estimation in pigs

Authors: *A. GIANNOTTI[1], M. CERADINI[2], S. MUSCO[3], F. BERNINI[4], G. DEL POPOLO[3], S. MICERA[5,2];
[1]Scuola Superiore Sant'Anna, Pisa, Italy; [2]Sant'Anna Sch. of Advanced Studies, Pisa, Italy; [3]Careggi Univ. Hosp., Florence, Italy; [4]Sant'Anna school of Advanced Studies, Pisa, Italy; [5]Swiss Federal Inst. of Technol., Lausanne, Switzerland

Abstract: Neurogenic lower urinary tract dysfunctions can impair physiological storage and elimination of urine, profoundly affecting patients' quality of life. Neuroprosthetic devices showed effectiveness in treating lower urinary tract symptoms, such as incontinence and incomplete bladder emptying. However, existing commercial devices use continuous and open-loop stimulation paradigms lacking real-time adaptability to patients' needs, which may cause micturition dysfunction due to neural adaptation. Closed-loop stimulation paradigms have been shown to increase bladder capacity and micturition efficiency compared with continuous stimulation, but robust, real-time decoding strategies of bladder fullness state are needed. Here, we propose a decoding algorithm that uses intraneural pudendal nerve signals to predict bladder pressure, allowing real-time estimation of bladder fullness and adaptation of stimulation paradigms to patients' needs. We performed surgical exposure of the left pudendal nerve in an anesthetized female farm pig (30-32kg, 3-4 months old) using a transgluteal approach. Subsequently, we implanted two 16-channel transverse intrafascicular multi-channel electrodes. A 6-Fr dual lumen water-filled catheter was inserted transurethrally into the bladder enabling filling and intravesical pressure measurement. A 10-Fr water-filled catheter was placed in the rectum to measure abdominal pressure. Detrusor pressure was estimated as the difference between intravesical and abdominal pressure. The bladder was drained, and pressure transducers calibrated according to the International Continence Society standardization. Sterile saline solution was then continuously infused into the bladder with a filing rate of 50 ml/min, while intraneural pudendal nerve activity was recorded. Saline infusion was stopped upon the visual observation of urination or urine leakage. Detrusor pressure was predicted bladder pressure using a custom-developed deep-learning-based algorithm. The algorithm used the peak-to-peak amplitude of filtered pudendal intraneural signals in the range of 300-1000 Hz as input. The results obtained in predicting detrusor pressure from the neural signal surpassed the chance level, with an average predicted value exceeding the 80th percentile of the ground-truth pressure value. For each time instant, the algorithm considered approximately 1s of neural data preceding the instant under consideration making this algorithm potentially suitable for real-time applications. Our findings pave the way towards implementing a real-time adaptive closed-loop stimulation protocol for pudendal nerve modulation.

Disclosures: A. Giannotti: None. **M. Ceradini:** None. **S. Musco:** None. **F. Bernini:** None. **G. Del Popolo:** None. **S. Micera:** None.

Poster

PSTR029: Advances in Brain Computer Interfaces

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Topic: E.05. Brain-Machine Interface

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T&C Chen Brain-machine Interface Center
NIH/NINDS Grant U01NS098975
NIH/NINDS Grant U01NS123127
Neilsen Postdoctoral Fellowship Research Grant 731621

Title: Long-term stability over 2,800 days of stimulation and recording through SIROF arrays in a human participant

Authors: *S. DARCY[1], D. A. BJANES[1], L. BASHFORD[2], K. PEJSA[1], B. LEE[3], C. LIU[4], R. A. ANDERSEN[5];
[1]Caltech, Pasadena, CA; [2]Biol. and Biol. Engin., Caltech, Pasadena, CA; [3]Neurosurg., USC, San Marino, CA; [4]USC, Los Angeles, CA; [5]BBE, Calif Inst. of Technol., Pasadena, CA

Abstract: Long-term stability of implanted microelectrode arrays is a fundamental requirement for the viability of brain-machine interfaces (BMIs) as clinical and assistive devices. BMI devices hold significant promise to accomplish a variety of clinical outcomes by capturing neural activity and applying signal processing to decode an extraordinary amount of detailed information: motor planning and intent, high-level cognitive goals, speech and language, and dysregulated neural activity. Furthermore, somatosensory brain-machine interfaces (SBMIs) can inject information into cortical networks via electrical stimulation, creating novel sensory percepts by modulating the activity of neural populations in the brain. One tetraplegic participant was implanted in Nov. 2016 with two NeuroPort microelectrode arrays (SIROF - sputtered iridium oxide film) in somatosensory cortex and microelectrode arrays (Platinum - Pt) in posterior partial cortex (PPC) and ventral pre-motor (PMv) areas. Quantitative measurements were obtained throughout the duration of study, such as 1 kHz impedance, signal-to-noise ratio and RMS noise. A variety of spatiotemporal electrical stimulation patterns were used to elicit naturalistic somatosensory percepts from the arm and hand throughout the study. Total stimulation charge delivered per channel and qualitative verbal reports of evoked sensations from the participant were quantified. This work quantified the stability and reliability of the recording interface and evoked somatosensory percepts via electrical stimulation over the duration of implant until the present time (currently ~2800 days). Nearly half of the stimulation channels continued to elicit somatosensory percepts throughout that duration. About a third of the channels on the SIROF array also maintained clear single-unit neural activity through the same duration (SNR >2). Both results demonstrate a high degree of stability and reliably over nearly 8 years of implantation. This work builds on our investigation of the long-term stability of implanted BMI devices, demonstrating that SIROF technology has the ability to effectively both record and stimulate for nearly twice as long as previously reported in the literature. These findings are significant advances toward development of state-of-the-art sensory BMIs and validate long term performance over multi-year BMI clinical trials.

Disclosures: S. Darcy: None. **D.A. Bjanes:** None. **L. Bashford:** None. **K. Pejsa:** None. **B. Lee:** None. **C. Liu:** None. **R.A. Andersen:** None.

Poster

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Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: E.05. Brain-Machine Interface

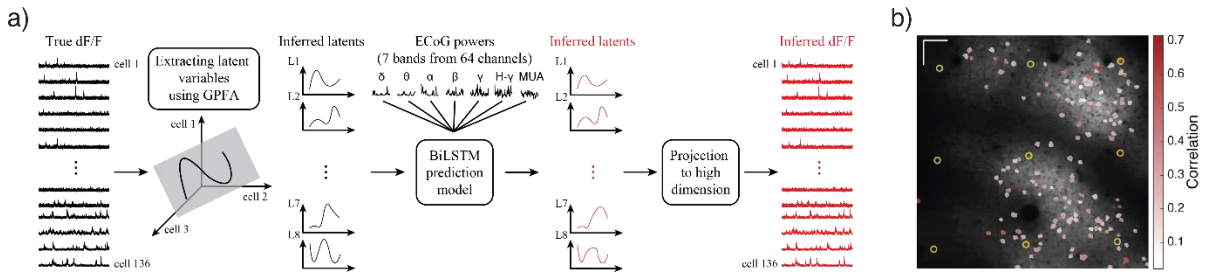
Support: ONR N000142012405, N000142312163 and N000141912545
NSF ECCS- 2024776, ECCS-1752241, and ECCS-1734940
NIH EY029466, R21 EB026180, and DP2 EB030992
NIH R01 NS091010A and R01 DC014690

Title: Prediction of Cellular Calcium Activity at Depth from Surface Potentials Recorded by High-Density Transparent Graphene Arrays

Authors: *M. RAMEZANI[1], J.-H. KIM[2], C. REN[4], A. ALOTHMAN[2], V. GILJA[2], T. KOMIYAMA[3], D. KUZUM[2];
[2]Electrical and Computer Engin., [3]Ctr. for Neural Circuits and Behavior Rm 304, [1]Univ. of California San Diego, La Jolla, CA; [4]Inst. of Neurosci., Chinese Acad. of Sci., Shanghai, China

Abstract: The ability to record neuronal activity from deep brain structures without invasive procedures is a pivotal advancement for both basic neuroscience research and clinical applications. Current methodologies predominantly rely on invasive probes or surface arrays that either do not provide the necessary depth or compromise spatial resolution. Our research introduces a novel application of high-density, transparent graphene arrays coupled with two-photon calcium imaging to address these limitations. This study specifically focuses on leveraging the unique properties of graphene, including its transparency and artifact-free nature, to record high-fidelity signals from the cortical surface while simultaneously performing optical imaging of underlying neuronal activity. By employing a cross-modality inference model that integrates surface electrophysiological data and two-photon calcium imaging, we decode the calcium activity of individual neurons within layer 2/3 of the mouse visual cortex. Our approach uses a dimensionality reduction technique (GPFA) to identify low-dimensional representations of high-dimensional optical data. This is followed by employing a BiLSTM network to predict latent variables from recorded surface potentials. The inferred latents are then used to reconstruct the activity of individual neurons, demonstrating our model's capacity to predict deep cortical activity from surface recordings effectively. Our findings suggest significant potential for enhancing brain-computer interfaces and advancing our understanding of neural dynamics in both health and disease states, such as in neurodegenerative disorders. Future studies will focus on refining our decoding techniques and expanding the applicability of our models to other brain regions and different animal models.

Figure 1. Decoding cellular calcium activity from surface potentials. (a) Schematic of the single-cell decoding model. (b) Decoding performance (correlation) for all the 136 cells with their locations outlined in the FoV.



Disclosures: **M. Ramezani:** None. **J. Kim:** None. **C. Ren:** None. **A. Alothman:** None. **V. Gilja:** None. **T. Komiyama:** None. **D. Kuzum:** None.

Poster

PSTR029: Advances in Brain Computer Interfaces

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Program #/Poster #: PSTR029.04/G29

Topic: E.05. Brain-Machine Interface

Support: NIH DP2MH126378
ONR YIP N00014-19-1-2128

Title: Nonlinear dynamical modeling of multimodal neural population activity with real-time inference

Authors: *E. ERTURK, M. M. SHANECHI;
Electrical and Computer Engin., USC, Los Angeles, CA

Abstract: Improving the robustness and performance of brain-computer interfaces (BCIs) can benefit from incorporating multiple neural modalities into the decoding algorithm. However, a major challenge in designing such a multimodal model arises because these modalities, such as spiking activity and field potentials, are often recorded with different sampling rates, or can even be missing at some time-steps due to measurement failures. Further, while nonlinear deep learning models hold much promise, performing real-time multimodal inference and information fusion with these models remains challenging. Recent deep learning-based approaches assume the same timescale and no missing samples across modalities and have non-causal inference architectures that pose a challenge to real-time decoding. Indeed, prior real-time multimodal inference algorithms for neural data have been based on linear dynamical systems instead. Here, we develop a novel nonlinear multiscale dynamical model of neural activity that can nonlinearly aggregate information across multiple modalities with different distributions, distinct timescales, and/or missing samples over time, while supporting real-time/causal estimation of multiscale latent factors. We first validate our model on nonlinear multimodal stochastic Lorenz attractor simulations and show that it can successfully aggregate information across modalities to improve the reconstruction accuracy of the true latent dynamics. Next, we apply our model to a non-human primate (NHP) motor cortical dataset consisting of discrete spiking activity and

continuous LFP recordings during a random target-reaching task. We demonstrate that our model better decodes the target behavior compared to single-scale models and to other linear or nonlinear multiscale baseline models. Overall, this model can provide a new tool to study multiscale neural dynamics and to advance BCI applications with real-time multimodal decoding.

Disclosures: **E. Erturk:** None. **M.M. Shanechi:** None.

Poster

PSTR029: Advances in Brain Computer Interfaces

Location: MCP Hall A

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Program #/Poster #: PSTR029.05/G30

Topic: E.05. Brain-Machine Interface

Support: NIH R01MH123770
ONR YIP N00014-19-1-2128
ARO MURI W911NF-16-1-0368
NSF CRCNS, IIS-2113271

Title: Optimal non-causal extraction of behaviorally relevant neural dynamics

Authors: *O. G. SANI, M. M. SHANECHI;
Electrical and Computer Engin., USC, Los Angeles, CA

Abstract: Given the distributed representation of various behaviors in neural activity, accurate isolation and modeling of neural dynamics that are relevant to specific behaviors has received growing interest in neuroscience. Preferential subspace identification, i.e., PSID (Sani et al, 2021), is a method for joint neural-behavioral modeling. It dissociates behaviorally relevant neural dynamics from other neural dynamics while prioritizing the extraction of the former. However, PSID, and subspace identification (SID) methods in general, aim to aggregate information casually. As such, these methods do not attempt to incorporate behaviorally relevant information that may appear in neural data with a lag relative to the behavior, i.e., in the future of behavior. A shift in behavior data during training can address this issue to some extent. However, as we will show, even with such a shift, SID methods in general learn models that are not optimal for non-causal estimation using the entire neural time-series data both in the past and future. We then show that in the case of PSID, this challenge can be addressed by leveraging the existence of two time series: behavior and neural data. We develop a method that enables optimal non-causal estimation of behaviorally relevant latent states from neural time-series. This is done by adding a backwards model that adds future behaviorally relevant information into the PSID model. We validate our approach in numerical simulations and demonstrate its application in real neural data. Our extension of PSID enables more accurate estimation of behaviorally relevant states when non-causal estimation is of interest or admissible, for example when neural data from a complete trial is to be used.

Disclosures: **O.G. Sani:** None. **M.M. Shanechi:** None.

Poster

PSTR029: Advances in Brain Computer Interfaces

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Topic: E.05. Brain-Machine Interface

Support: NIH DP2-MH126378
NIH R01MH123770
ONR YIP N00014-19-1-2128

Title: Input-driven nonlinear dynamical modeling of neural-behavioral data

Authors: *P. VAHIDI[1,2], O. G. SANI[3], M. M. SHANECHI[3];
[1]USC, Los Angeles, CA; [2]Electrical and Computer Engineering, University of Southern California, Los Angeles, CA; [3]Electrical and Computer Engin., USC, Los Angeles, CA

Abstract: Neural population activity is a high-dimensional and temporally-structured signal that arises due to both intrinsic properties of the population as well as external inputs to it. For example, external inputs can consist of measured sensory stimuli, upstream activity, or neurostimulation. Jointly modeling inputs, neural activity, and behavioral measurements can reveal intrinsic behaviorally relevant neural dynamics that may be missed otherwise (Vahidi, Sani, Shanechi, 2024). However, input-driven dynamical modeling of neural-behavioral data has so far been largely limited to linear approaches. Despite their power, linear models may not capture the full complexity of neural computations underlying behavior. To address this challenge, we develop a new nonlinear input-driven dynamical model of neural-behavioral data using recurrent neural networks (RNN). Our method simultaneously: i) captures nonlinearity in input-neural-behavioral data, ii) disentangles intrinsic neural dynamics from input dynamics, and iii) dissociates the intrinsic behaviorally relevant neural dynamics from other neural dynamics. We first validate our method using numerical simulations and then demonstrate its application in real neural data recorded from non-human primates (NHPs). The new nonlinear method achieves the above dissociation capabilities while significantly improving the fit to neural-behavioral data compared with linear methods. This novel method can enable studies of how input-driven and intrinsic nonlinear neural computations give rise to behavior.

Disclosures: **P. Vahidi:** None. **O.G. Sani:** None. **M.M. Shanechi:** None.

Poster

PSTR029: Advances in Brain Computer Interfaces

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Topic: E.05. Brain-Machine Interface

Support: ONR YIP contract N00014-19-1-2128
ARO MURI W911NF-16-1-0368
NIH R01MH123770

Title: Unsupervised learning of multiscale switching dynamical systems

Authors: *D. KIM, C. Y. SONG, M. M. SHANECHI;
Electrical and Computer Engin., USC, Los Angeles, CA

Abstract: Neural population activity can exhibit regime-dependent non-stationarity in the form of switching dynamics, such as dynamics that depend on task regimes. Thus, unsupervised learning of switching dynamical systems has received much attention in recent years. To date, these approaches have focused on unsupervised learning from a single neural modality, either from Gaussian continuous modalities such as field potentials or from Poisson spiking modalities. However, in many datasets, multiple neural modalities are available simultaneously. To address these cases, we develop an unsupervised algorithm for learning switching dynamical systems from multimodal data, which has remained elusive so far. Our recent work on learning switching dynamical systems from unimodal Poisson data has shown that a new inference algorithm based on deterministic sampling -- termed Poisson cubature filter (PCF) -- can improve the accuracy of learning compared with Laplace-based approximations that are typically used (Song & Shanechi, 2023). Here, we extend our approach to support multiple neural modalities simultaneously. To do so, we derive a new deterministic approximation based multiscale filter and use it to enable learning of switching dynamical systems from multimodal Poisson-Gaussian data. We first validate our method on numerical simulations and demonstrate that our model results in better latent factor and regime estimation compared to single scale methods and Laplace approximation based methods. Next, we apply our method to a non-human primate (NHP) motor cortical dataset of discrete spiking activity and continuous local field potential activity to demonstrate that our method successfully achieves multimodal fusion in switching dynamical systems to yield better behavior decoding over prior unimodal switching approaches. This new method can help study switching dynamics across different spatiotemporal brain scales and develop brain-computer interfaces that address regime-dependent non-stationarity.

Disclosures: D. Kim: None. **C.Y. Song:** None. **M.M. Shanechi:** None.

Poster

PSTR029: Advances in Brain Computer Interfaces

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Topic: E.05. Brain-Machine Interface

Support: New Venture Fund NVF-FFOR 023367-2024-02-01
NIH R01MH123770
NSF CRCNS IIS-2113271

Title: Dynamical modeling of brain network response to DBS using calcium imaging

Authors: *E. BILGIN[1], E. ERTURK[1], B. J. VAN DEN BOOM[2], I. WILLUHN[2], M. M. SHANECHI[1];
[1]Electrical and Computer Engin., USC, Los Angeles, CA; [2]Netherlands Inst. of Neurosci., Amsterdam, Netherlands

Abstract: Deep brain stimulation (DBS) can serve as a treatment for several neurological and neuropsychiatric disorders such as obsessive-compulsive disorder by modulating brain activity. To understand the effects of DBS and improve the precision of such neuromodulation, accurate input-output modeling of brain network responses to DBS input is beneficial. Such input-output modeling may also facilitate the development of brain-computer interfaces for closed-loop neuromodulation. With these goals in mind, we developed a dynamical input-output model that can predict the dynamic brain network response to different DBS parameters from calcium imaging recordings. Calcium imaging offers an opportunity for understanding the brain response as it does not suffer from DBS stimulation artifacts unlike electrophysiological recordings. To validate our method, we analyzed a one-photon calcium imaging dataset that monitors the brain activity of freely-moving mice while stimulating the ventral internal capsule with DBS parameters that were systematically varied in amplitude, pulse width, and frequency. We show that our models can successfully learn the effect of different DBS parameter values. Further, we show that our input-driven models can forecast the network response into the future and study the time-course of this response. These results can inform how brain networks respond to DBS and may guide the development of closed-loop DBS therapies for neurological and neuropsychiatric disorders.

Disclosures: E. Bilgin: None. **E. Erturk:** None. **B.J. van den Boom:** None. **I. Willuhn:** None. **M.M. Shanechi:** None.

Poster

PSTR029: Advances in Brain Computer Interfaces

Location: MCP Hall A

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Program #/Poster #: PSTR029.09/G34

Topic: E.05. Brain-Machine Interface

Title: Ezmsg: a high-performance python framework for real-time neural signal processing in neuroscience and bci applications

Authors: *G. MILSAP[1], **C. BOULAY**[2], P. PERANICH[1], H. MARTINEZ[1], M. ANGRICK[3], J. DUNANT[2], Q. RABBANI[3], S. LUO[3], D. CANDREA[3], J. B. ZIMMERMANN[2], N. E. CRONE[3];

[1]Res. and Exploratory Develop., Johns Hopkins Univ. Applied Physics Lab., Laurel, MD; [2]Wyss Ctr. for Bio and Neuroengineering, Geneva, Switzerland; [3]Johns Hopkins Univ., Baltimore, MD

Abstract: ezmsg is an open-source [1] and permissively-licensed pure-Python (with no dependencies) framework for fast prototyping of real-time neural signal processing applications, particularly in neuroscience and brain-computer interfacing (BCI). This framework was introduced to complement the current landscape of similar technologies (e.g. LabGraph, NeuroPype, ROS) which can be difficult to set up (requiring many compiled binaries) and difficult to instantiate within offline analysis notebooks/scripts/frameworks. ezmsg uses a directed acyclic graph (DAG) structure that allows for components and sub-graphs to run in separate processes; graphs may be modified while the pipeline is running. ezmsg achieves high performance by using shared memory for message passing between processes, handling tens of thousands of messages per second and data throughput of tens of GB/s. First-party packages include components for sources and sinks including neurophysiology hardware and interprocess communication protocols such as LabStreamingLayer, ZeroMQ, ROS2, and web sockets. Additionally, and perhaps most importantly, ezmsg has first-party components for signal processing that are tested and portable to other contexts; a unique capability in this space that aids the transition from prototype to regulated software that doesn't require the ezmsg framework to deploy. ezmsg has been used in research on implanted BCI systems; in particular the CORTICOM clinical trial [2-3], high-framerate digital holographic imaging, and is being used in the INTRECOM and W-ICONS clinical trials with ABILITY implant technology.
[1] https://github.com/iscoe/ezmsg
[2] Luo, Sl., Angrick, M., Coogan, C, et al. Stable Decoding from a Speech BCI Enables Control for an Individual with ALS without Recalibration for 3 Months. Advanced Science 10, 35 (2023). https://doi.org/10.1002/advs.202304853
[3] Angrick, M., Luo, S., Rabbani, Q. et al. Online speech synthesis using a chronically implanted brain-computer interface in an individual with ALS. Sci Rep 14, 9617 (2024). https://doi.org/10.1038/s41598-024-60277-2

Disclosures: G. Milsap: None. **C. Boulay:** None. **P. Peranich:** None. **H. Martinez:** None. **M. Angrick:** None. **J. Dunant:** None. **Q. Rabbani:** None. **S. Luo:** None. **D. Candrea:** None. **J.B. Zimmermann:** None. **N.E. Crone:** None.

Poster

PSTR029: Advances in Brain Computer Interfaces

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Topic: E.05. Brain-Machine Interface

Support: NIH NINDS U01NS123125
NIH NINDS R01NS121079
NIH NINDS UH3NS107714
DOE DE-SC0023112

Title: Neural Data Transformer 3: A foundation model for motor cortical decoding

Authors: ***J. YE**[1], J. MAYO[5], A. L. SMOULDER[2], X. MA[10], H. MAO[6], R. H. CHOWDHURY[7], E. R. OBY[7], A. P. BATISTA[8], S. M. CHASE[3], A. G. ROUSE[12], C. M. GREENSPON[13], L. E. MILLER[11], N. G. HATSOPOULOS[14], A. SCHWARTZ[15], J. L. COLLINGER[6], L. WEHBE[4], R. A. GAUNT[9];
[2]Dept. of Biomed. Engin., [3]Neurosci. Inst., [4]Machine Learning Dept., [1]Carnegie Mellon Univ., Pittsburgh, PA; [5]Dept. of Ophthalmology, [6]Univ. of Pittsburgh, Pittsburgh, PA; [7]Univ. of Pittsburgh, Pittsburgh, PA, ; [8]Bioengineering, [9]Physical Med. and Rehabil., Univ. of Pittsburgh, Pittsburgh, PA; [10]Dept. of Neurosci., [11]Neurosci., Northwestern Univ., Chicago, IL; [12]Neurosurg., Univ. of Kansas Med. Ctr., Kansas City, KS; [13]Dept. of Organismal Biol. & Anat., [14]Univ. of Chicago, Chicago, IL; [15]Neurobio., Univ. of Pittsburgh Dept. of Neurobio., Pittsburgh, PA

Abstract: Motor neuroscience has long quantified the relation between intracortical activity and behavior with individual datasets. This constrained scope yields models that are often not robust across experiments and sometimes even underfit within experiments due to insufficient data. These limits can be surpassed by transfer learning, particularly in deep networks, where models are not fit from scratch but adapted from models previously trained (pretrained) with data from other experimental sessions, subjects, and tasks. In non-neuroscientific domains, similar narratives of gains from pretraining and transfer have concluded in the pursuit of generalist models that train and perform well on breadths of data. Past a certain scale, these generalists functionally serve as foundational models for whole subfields, accelerating modeling for nearly all downstream datasets.
We accordingly train Neural Data Transformer 3 (NDT3) as an intracortical motor foundation model, with 4000 hours of paired population activity and motor covariates from over 30 monkeys and humans from 10 labs (humans were enrolled in clinical trials for sensorimotor BCIs). This data includes behavior spanning reaching, grasping, and finger motion, both under BCI and native limb control. We test the hypothesis that NDT3's diverse pretraining enables competence across varied BCI applications, evaluating performance both with subject or task data that are seen by the pretrained model, and novel subjects performing novel tasks collected in different labs. NDT3 is a competent generalist across motor tasks: with minutes to a few hours of a new task, NDT3 far outperforms specifically prepared multi-session, single-task models. For even longer datasets, NDT3 matches the performance of single-task experts. These properties suggest NDT3 as a candidate for the first widely available model to improve arbitrary motor decoding from intracortical data.

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even if those funds come to an institution.; Blackrock Neurotech. F. Consulting Fees (e.g., advisory boards); Blackrock Neurotech, Neurowired.

Poster

PSTR029: Advances in Brain Computer Interfaces

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.11/G36

Topic: E.05. Brain-Machine Interface

Support: T32 NS121763
NIH NS122333
NIH NS107714

Title: Finding The Groove in Neural Space

Authors: *R. BHATT[1,2], D. E. SHEETS[3], J. E. DOWNEY[4], H. MERCHANT[5], C. M. GREENSPON[6];
[1]Univ. of Chicago, Chicago, IL; [2]Committee in Computational Neuroscience, University of Chicago, Chicago, IL; [3]Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL; [4]Dept. of Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL; [5]Inst. de Neurobiologia UNAM, Queretaro, Mexico; [6]Dept. of Organismal Biol. & Anat., Univ. of Chicago, Chicago, IL

Abstract: A fundamental element of coordinating periodic movements is rhythm. From locomotive actions, such as walking or swimming, to more complex actions, such as dancing or playing an instrument, periodic movements require precise synchronization of sequential actions. Although substantial research has explored the neural underpinnings of broad cyclic movements like locomotion in preclinical models, there remains a gap in understanding how these rhythms are represented in humans and how they extend to more complex movements. In this present study, we investigated the neural representations underlying rhythmic hand movements in the human sensorimotor cortex of participants with intracortical implants in the primary somatosensory (S1) and motor (M1) cortices. We sought to understand how M1 might encode rhythm and characterize the dynamics of this encoding at both the single-neuron and population levels. Participants were instructed to tap their index finger in tandem with an auditory cue that played at different frequencies. We constructed a range of tasks, in which we presented participants with distinct groups of frequencies and a continuous range of frequencies. Future experiments will include sequences of frequencies that represent syncopated rhythms. At the single-neuron level, we found subsets of neurons across M1 and S1 that were either phase-locked, frequency-tuned, both, or neither. However, we found population activity to best capture the encoding of rhythm across tasks and frequencies. In particular, we found a low-dimensional representation in the neural state space that exhibited rotational dynamics. Within this neural manifold, or groove, we also identified an axis of speed which separated the rotations by frequency. Overall, we found the presence of rotations to be indicative of the oscillatory nature of the taps and discovered that the geometry and location of these rotations in the manifold

changed based on frequency. We further characterized changes in the rotational dynamics as the frequency transitioned from one to another. Therefore, in this study we showed that at the population level there exists an underlying neural manifold in the sensorimotor cortex that contains rotational dynamics for rhythmic hand movements.

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Poster

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Program #/Poster #: PSTR029.12/G37

Topic: E.05. Brain-Machine Interface

Title: Deciphering Neural Dynamics: LSTM Networks and Gamma Band Modulation in Movement Analysis

Authors: *X. SHAO[1], S. SUNDARAM[4], R. MARTIN DEL CAMPO VERA[1], M. PARRA[2], S. KELLIS[5], B. LEE[3];
[2]Neurosurg. / Bioengineering, [3]Neurosurg., [1]USC, Los Angeles, CA; [4]Keck Sch. of Med., Los Angeles, CA; [5]Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: Recent studies have highlighted the significant role of gamma-band activity in motor control and cognitive processes related to movement planning and execution. Concurrently, advancements in neural network applications, particularly in deciphering movement-related neural signals, have opened new avenues in understanding the brain's complex neuroelectric dynamics. These neural networks, leveraging deep learning algorithms, have shown promise in accurately modeling and predicting motor activities based on neural oscillations, marking a crucial step forward in the intersection of computational neuroscience and artificial intelligence. This project builds upon these foundational studies, aiming to further explore and elucidate the intricate relationship between gamma-band modulation and movement through the innovative use of Long Short-Term Memory (LSTM) networks. Utilizing intracranial stereotactic electroencephalogram (sEEG) recordings of deep brain regions, we conducted a comprehensive analysis of gamma-band modulation during instructed left/right/hold movement tasks. To do this, we developed a Python-based data processing pipeline for signal cleaning, preprocessing, and spectral analysis and innovated a re-referencing technique to minimize signal contamination. Furthermore, we explored the potential of LSTM networks by employing spectrograms and demixed Principal Component Analysis (dPCA) for feature extraction, aiming to classify neural modulation based on hand movement direction. Our findings reveal significant directional-related modulation in the gamma band during movement execution, particularly in regions traditionally not associated with movement such as the insula. The application of dPCA revealed the temporal dynamics of gamma band under different movement conditions. These dynamics, which can be decoded using LSTM networks, achieved a 70% accuracy in decoding directional-

related neural modulation, showcasing the potential of deep learning in interpreting complex neural dynamics. The project underscores the pivotal role of gamma-band analysis and LSTM networks in advancing our comprehension of neural mechanisms underlying movement. These insights pave the way for significant improvements in brain computer interface (BCI) technologies, marking an inspiration to computational neuroscience and neural engineering fields.

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Poster

PSTR029: Advances in Brain Computer Interfaces

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.13/H1

Topic: E.05. Brain-Machine Interface

Title: Exploring error-related potentials in adaptive brain-machine interfaces: investigation of a generic classifier based on simulated data

Authors: A. XAVIER FIDÊNCIO[1], ***C. KLAES**[2], I. IOSSIFIDIS[3];
[1]Neurosurgery/KlaesLab, Ruhr-University Bochum/University Hosp. Knappschaftskrankenhaus Bochum, Bochum, Germany; [2]Knappschaftskrankenhaus Bochum, Bochum, Germany; [3]Inst. of Informatics, Hochschule Ruhr West, Bottrop, Germany

Abstract: Error-related potentials (ErrPs) play a crucial role in the development of adaptive brain-computer interfaces (BCIs). These brain signals are not only generated upon self-made errors but also in response to mistakes made by the BCI itself, thus serving as a natural and intrinsic feedback signal for developing adaptive systems. However, the effective utilization of ErrPs heavily relies on their accurate single-trial classification, which typically requires an extensive calibration session to collect sufficient data for training a subject-specific classifier. This process is not only time-consuming but also exhausting for subjects. In our research, we systematically generated training instances using the open-source toolbox SEREEGA and evaluated the performance of a generic classifier on both simulated and real-world datasets. Our results indicate that the generic classifier performs comparably to a leave-one-subject-out approach, demonstrating promising generalization capabilities across subjects and datasets. Furthermore, by utilizing SEREEGA, we can systematically vary simulation parameters to account for variations in ErrP generation, enabling systematic validation of closed-loop setups. This approach proposes the use of ErrPs to enhance performance and allows establishing boundary conditions for successful closed-loop applications.

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Poster

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Program #/Poster #: PSTR029.14/H2

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01NS109257

Title: Improving intracortical BCI performance by constraining velocity control to discrete selections

Authors: *P. I. ALCOLEA[1], Z. C. DANZIGER[2], L. E. MILLER[3], K. BODKIN[3], X. MA[4]; [1]Florida Intl. Univ., Miami, FL; [2]Rehabilitation/Biomedical Engin., Emory Univ., atlanta, GA; [3]Neurosci., Northwestern Univ., Chicago, IL; [4]Dept. of Neurosci., Northwestern Univ., Chicago, IL

Abstract: Nearly all intracortical brain computer interface (iBCI) cursor control decoders translate neural activity into a continuum of possible velocities ("continuous velocity" decoding). Instead, we hypothesize that by constraining the velocity commands to a small set of discrete selections performance would be improved because its ability to simplify the acquisition of cursor control. Thus, we created the discrete direction selection (DDS) decoder that constrains decoded cursor velocity to the cardinal directions or stopping, and demonstrated it outperforms the most common continuous velocity decoders in cursor control. We assessed user performance with the decoders using the joint-angle BCI (jaBCI), a non-invasive human-in-the-loop iBCI model (Awasthi et al. 2022), and a monkey using an iBCI. In the jaBCI model 48 human subjects across four repeat visits were divided among one of four different decoders: 1) the classic velocity Kalman filter (vKF, Wu et al. 2002) that determines velocity through a linear weighting of prior cursor kinematics and current neural firing. 2) The ReFIT decoder (Gilja et al. 2012) that adds to the vKF model implicit information about online subject intention during calibration. 3) A population vector decoder with assisted calibration (DR-A, Inoue et al. 2018) that is an affine map between neuron firing rates to cursor velocity. 4) The DDS decoder. DDS users outperformed the other decoders by a substantial margin (93%, 56%, 39%, and 26% targets hit in DDS, DR-A, ReFIT, and vKF groups, ANOVA $p < 0.001$). In a follow up study, a monkey used an iBCI alternating between the DDS decoder and the Wiener filter decoder (WF, an extended version of DR-A that incorporates 400 ms of neural activity history into its velocity predictions, Wu et al. 2006) on 7 different days. Results showed means of 61% for DDS and 37% targets hit for WF ($p < 0.001$, two-tailed paired t-test). Both the jaBCI subjects and monkey subject were evaluated on the number of target hits on a 2D, 8-target, center out cursor task and both revealed that DDS subjects hit targets faster than other decoders. However, the speciic reason for DDS's superior performance isn't clear. What is known is that DDS cursor control had less turns, a simpler path tortuosity, lower velocities, and was the second best at stopping. This indicates to us that DDS overperformance over all "continuous velocity decoders" may be due to a cursor stabilizing, as micro-changes in neurons are less probable to effect the command. Thus, discrete control may be preferable for continuous tasks then continues control.

Disclosures: **P.I. Alcolea:** None. **Z.C. Danziger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US 011625099B2. **L.E. Miller:** None. **K. Bodkin:** None. **X. Ma:** None.

Poster

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Program #/Poster #: PSTR029.15/H3

Topic: E.05. Brain-Machine Interface

Support: NIH NEI UG1EY032039
T&C Chen BMI Center
Boswell Foundation

Title: Duration-modulated neural population dynamics in humans during BMI controls

Authors: *F. YIN[1], C. GUAN[2], J. GAMEZ[2], E. R. ROSARIO[3], C. LIU[4], A. BARI[5], R. A. ANDERSEN[2];
[2]Div. of Biol. and Biol. Engin., [1]Caltech, Pasadena, CA; [3]Res. Inst., Casa Colina Hosp. and Centers for Healthcare, Pomona, CA; [4]Dept. of Neurolog. Surgery, Keck Sch. of Med. of USC, Los Angeles, CA; [5]Dept. of Neurosurg., David Geffen Sch. of Med. at UCLA, Los Angeles, CA

Abstract: The autonomous dynamical systems hypothesis (aDSH) describes the motor cortex as a pattern generator where latent neural states unwind from initial conditions along known dynamics while staying agnostic to external inputs. The aDSH has been demonstrated comprehensively in able-bodied non-human primates performing reach tasks. Visually guided brain-machine interface (BMI) tasks in tetraplegic humans, on the other hand, lack the proprioceptive feedback present in able-bodied subjects, creating a more ideal setting for aDSH. Here we present results of neural population dynamics modulated by the duration of attempted reaches in BMI tasks as evidence inconsistent with aDSH.
We recorded single-unit activity from two tetraplegic human participants implanted with intracortical NeuroPort Arrays as part of a clinical trial. Participant 1 was implanted with one array in the hand knob area of the left motor cortex and one in the left posterior parietal cortex (PPC). Participant 2 was implanted with two arrays in the hand knob area of the left motor cortex and two in the left PPC. Only data from their motor cortices were used for this study.
We designed two variations of visually guided cursor reach tasks based on the center-out task: a ballistic-sustained version where the decoder gain varied by trial and a near-far version where the target distance varied by trial. We modeled aDSH with linear Gaussian state space models (LGSSMs), which learned attractor vector fields and neural trajectories with initial outward bursts followed by inward return paths in the latent space for both ballistic and sustained reaches. Given the same initial conditions of the two reach types, aDSH would predict the same outcome. However, we found that the return paths of sustained reaches slowed down significantly. Near-far center-out trials produced similar behaviors. These results show inconsistency with the aDSH

model. Further, previous studies showed that visual feedback only weakly affects the motor cortex. Since visual feedback is the only form of external stimuli perceived by our participants during the tasks, our results suggest the presence of task-relevant inputs from beyond the motor cortex.

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Poster

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Program #/Poster #: PSTR029.16/H4

Topic: E.05. Brain-Machine Interface

Support: Weill Neurohub

Title: Tracking eye gaze and pupil dynamics to improve Brain-computer Interface (BCI) control

Authors: *H. YAN[1], N. NATRAJ[2], S. SEKO[2], Y. GRAHAM[3], R. MIAO[3], E. F. CHANG[4], K. GANGULY[3];
[1]Neurol., Univ. of California San Francisco, San Francisco, CA; [2]Neurol., Univ. of California, San Francisco, San Francisco, CA; [3]Neurol., UCSF, San Francisco, CA; [4]Univ. of California, San Francisco, Piedmont, CA

Abstract: Tracking eye gaze and pupil dynamics to improve Brain-computer Interface (BCI) control H. Yan, N. Natraj, S. Seko, Y. Graham, R. Miao, E.F. Chang, K. GangulyBrain-computer interfaces (BCIs) have drastically improved human-machine interaction by enabling direct neural control of devices, facilitating a multitude of tasks in closed-loop settings. Our study involved two tetraplegic participants: a male with a brain stem stroke and a female diagnosed with ALS and brainstem stroke. Each participant was implanted with a chronic ECoG array—128 channels and 256 channels, respectively—targeting the sensory and motor cortices. Both neural and ocular data are recorded as the participants are engaging in various cursor and robotic control tasks. Here, we specifically tracked eye gaze and pupil dynamics to understand and improve BCI control.Our analysis included spatial-temporal and phase analysis of different neural signal bands alongside ocular signals such as pupil diameter, changes in pupil diameter speed, saccades, and eye gaze points. We found significant correlations and phase synchronizations between the slow components (0.1 ~ 1Hz) of pupil diameter speeds and the slow components of both beta (13–30 Hz) and delta (0.5–4 Hz) bands. Importantly, an increase in pupil diameter, which signals heightened attention, was found to inversely correlate with global beta power. This suggests a dynamic relationship between attentional engagement and the suppression of global beta activity.Furthermore, our study found that eye gaze tracking can help us understand and enhance BCI control strategies. By analyzing gaze patterns, we identify how participants direct their attention and intent, thereby facilitating more intuitive BCI control. This dual approach of

integrating pupil dynamics and eye gaze offers a novel perspective in optimizing BCI systems, paving the way for more adaptive and user-centric interfaces.

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Poster

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Program #/Poster #: PSTR029.17/H5

Topic: E.05. Brain-Machine Interface

Support: UH3NS114439 (NINDS)

Title: Brain computer interface control of a communication board using attempted upper-limb gestures

Authors: *D. CANDREA[1], S. LUO[1], M. ANGRICK[2], K. NATHAN[2], C. COOGAN[2], G. W. MILSAP[3], S. SHAH[2], N. J. MARAGAKIS[2], M. VANSTEENSEL[4], F. TENORE[3], M. S. FIFER[3], N. F. RAMSEY[4], N. E. CRONE[2];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Neurol., Johns Hopkins Hosp., Baltimore, MD; [3]Res. and Exploratory Develop., Johns Hopkins Applied Physics Lab., Laurel, MD; [4]Neurol. and Neurosurg., UMC Utrecht Brain Ctr., Utrecht, Netherlands

Abstract: Brain-computer interfaces (BCIs) have the potential to restore communication for individuals facing severe movement and speech impairments by interfacing neural activity to various applications. In this study, we investigated the potential of a participant with ALS to control a communication board using attempted manual gestures. Specifically, we decoded the upper-limb sensorimotor representations from contralateral and ipsilateral gestures using a chronically implanted high-density electrocorticographic (ECoG) array, and mapped these to six different commands (Up, Down, Left, Right, Enter, Back) to control a communication board. Additionally, we found that contralateral cortical movement representations were stronger than ipsilateral, and that ipsilateral representations were stronger in premotor and motor cortices than in sensory cortex.

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Poster

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Program #/Poster #: PSTR029.18/H6

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01NS121079
Swiss National Science Foundation Grant P500PM_210800

Title: Motor cortex somatotopy influences control strategy success for human brain-computer interfaces

Authors: *N. G. KUNIGK[1,2,3], H. SCHONE[4,2], W. HOCKEIMER[4,2], C. GONTIER[4,2], A. F. TORTOLANI[5], N. G. HATSOPOULOS[5,6,7], J. E. DOWNEY[8], S. M. CHASE[9,3,10], M. BONINGER[4,11,2], B. DEKLEVA[4,2,3], J. L. COLLINGER[4,11,2,3,10];
[1]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA; [2]Rehab Neural Engineering Labs, Pittsburgh, PA; [3]Center for the Neural Basis of Cognition, Pittsburgh, PA; [4]Physical Med. and Rehabil., Univ. of Pittsburgh, Pittsburgh, PA; [5]Computat. Neurosci., Univ. of Chicago, Chicago, IL; [6]Organismal Biology and Anatomy, University of Chicago, Chicago, IL; [7]Neuroscience Institute, University of Chicago, Chicago, IL; [8]Dept. of Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL; [9]Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA; [10]Biomedical Engineering, Carnegie Mellon University, Pittsburgh, PA; [11]Bioengineering, University of Pittsburgh, Pittsburgh, PA

Abstract: The notion of a somatotopically organized motor cortex, with movements of different body parts being controlled by spatially distinct areas of cortex, is well known[1]. For the upper limb, more proximal movements are controlled by cortical areas closer to midline while distal movements are controlled by more lateral areas. However, more recent studies have challenged this notion[2]. This shift in perspective has significant implications, particularly for intracortical brain-computer interfaces (iBCIs). We sought to evaluate whether the location of the neural recordings, and thus the underlying somatotopy, has any impact on the imagery strategies that can enable successful iBCI control. Five people with cervical spinal cord injury were enrolled in an ongoing clinical trial of an iBCI. Participants had two electrode arrays (100 electrodes each) implanted in the arm and hand areas of motor cortex (C1, C2, P2, P4) or both in the hand area (P3) based on presurgical functional imaging. Neural data were recorded while participants attempted to perform movements of the hand, wrist, elbow, and shoulder. Some movements could not be performed overtly due to their injury. In P2, P3, and P4, electrode arrays that were located more medially recorded significantly more activity during attempted proximal arm movements (elbow, shoulder) than did lateral arrays, which captured more activity related to attempted distal arm movements (hand, wrist). For participants C1 and C2, the lateral array recorded significantly more distal than proximal arm movements, and the medial array was excluded from analysis due to limited signal quality. We next evaluated the relative contribution from the medial and lateral arrays to decoding accuracy assessed during calibration of an iBCI decoder for reaching tasks and for grasping tasks in P2, P3, and P4. For reaching, decoding accuracy was significantly greater using recordings from only the medial array as compared to the lateral array (P2, n=41 sessions; P3, n=44; P4, n=16; mean R^2 lateral vs medial $p < 0.05$ all; Wilcoxon rank sum test), which aligns with the expectation that more proximal movements are represented medially. For grasping, decoding accuracy was significantly greater using recordings

from the lateral array as compared to the medial array, except in P3 who has both arrays in the hand area (P2, n=41 sessions, mean R^2 lateral vs medial $p < 0.001$; P3, n=44, $p = 0.420$; P4, n=22, $p < 0.001$; Wilcoxon). These results demonstrate that classical concepts of somatotopy can have real consequences for iBCI use, and highlight the importance of considering somatotopy when planning iBCI implantation. 1. Penfield, W. & Boldrey, 1937. 2. Willet, F. R. *et al*., 2020.

Disclosures: **N.G. Kunigk:** None. **H. Schone:** None. **W. Hockeimer:** None. **C. Gontier:** None. **A.F. Tortolani:** None. **N.G. Hatsopoulos:** None. **J.E. Downey:** None. **S.M. Chase:** None. **M. Boninger:** 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.; Blackrock Microsystems. **B. Dekleva:** None. **J.L. Collinger:** 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.; Blackrock Microsystems.

Poster

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Topic: E.05. Brain-Machine Interface

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NSF Grant IOS-123213

Title: Decoding kinematic features from high-frequency surface potentials and single-unit activity in primate motor cortex

Authors: *A. ESTRADA BERLANGA[1], A. DUBEY[2], K. WINGEL[1], V. DINH[1], J. CHOI[3], J. VIVENTI[4], C.-H. CHIANG[5], C. WANG[6], B. PESARAN[7];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Ctr. For Neural Sci., Univ. of Pennsylvania, Philadelphia, PA; [3]New York Univ., New York, NY; [4]Biomed. Engin., Duke Univ., Durham, NC; [5]Duke Univ., Durnham, NC; [6]BME, Duke Univ., Durham, NC; [7]Neurosurg., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Decoding motor movement from brain activity is essential for advancing neuroprosthetic technologies for individuals with neurodegenerative disorders or injuries. This study explores the efficacy of decoding movement intent from electrical surface potentials and action potentials in motor cortices of non-human primates. Electrode technologies to record surface potentials and action potentials differ in their invasiveness and coverage. Surface potential electrodes are less invasive than action potential electrodes because they do not penetrate the cortical tissue and offer better spatial coverage of the cortical sheet. However, action potential electrodes offer better signal resolution and spatial coverage across the cortical

layers. Whether and how movement intent can be decoded within the cortex more accurately than from the cortical surface remains poorly understood.
Here, we decode surface potentials by implanting a uECoG electrode—a less invasive and robust modality—and decode action potentials by implanting a Neuropixels electrode in the motor cortex of two monkeys. The uECoG electrode had 244 gold contacts (200um size) spaced 750 um in a liquid-crystal polymer substrate. All contacts were recorded at 30 kHz sampling rate. The neuropixel electrode contained 960 TiN contacts (12 um size) spaced 20 um along a 10mm silicon shank. Of the 960 contacts, 384 contacts were selected for recording at 30 kHz sampling rate. Recordings from each electrode were obtained from the motor cortices of two macaque monkeys performing a free-reach behavioral task during separate experimental sessions. We then spatially registered the neuropixel recording site to the uECoG recording sites. Free-reach behavior was recorded with three cameras, analyzing the monkeys' reaches towards a wand at various orientations and distances. We computed the wrist's 3D position with computer vision techniques (DeepLabCut) and estimated three key wrist kinematic variables: absolute speed magnitude, directional velocity, and component-wise absolute speed. We extracted neural features—single-unit activity (SUA) from Neuropixels, Local Motor Potential (LMP), and spectral features from uECoG field potential signals—to predict kinematic variables and compared their performance. Our preliminary regression analysis reveals that power in high-gamma (70-250 Hz) uECoG signals correlates most strongly with reach kinematic variables. LMP and SUA features were less consistent across variables compared to high-gamma activity, suggesting surface potentials are a promising less invasive target than SUA for decoding motor intent in neuroprosthetic applications.

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Poster

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Topic: E.05. Brain-Machine Interface

Support: Brain Canada Foundation
Institut TransMedTech

Title: Decoding movement execution from the mesencephalic locomotor region (MLR) to establish a novel target for brain-computer interfaces (BCI).

Authors: *D. BURCHIELLI[1,2], M. BONIZZATO[1,2,3];
[1]Dept. of Electrical Engin., Polytechnique Montréal, Montreal, QC, Canada; [2]Mila - Québec AI Inst., Montréal, QC, Canada; [3]Dept. of Neurosciences, Univ. de Montréal, Montreal, QC, Canada

Abstract: Brain-computer interfaces (BCIs) allow real-time decoding of neural activity from the brain. Decoded activity is used to control external devices and to drive functional stimulation to reanimate paralyzed limbs, potentially restoring motor independence in individuals with impaired motor control. Traditionally, the preferred BCI source for movement intention has been the primary motor cortex (M1). However, the limited focus of motor BCI on M1 has restricted the decodable motor processes that can be leveraged in BCI applications. Subcortical regions involved in motor control may emerge as alternative or complementary targets for motor BCIs. We investigated in female Long Evans rats whether a midbrain region called the mesencephalic locomotor region (MLR) could serve as a target for BCIs to infer and predict movement intention. Although the MLR motor involvement has been previously investigated, the extent to which MLR regulates movement is still widely unknown, especially for motor control beyond locomotion. We implanted N=6 rats with 16 and 32-channel arrays in the two MLR nuclei, the cuneiform nucleus (CnF) and the pedunculopontine nucleus (PPN). The neural activity, along with the muscle activity (EMGs), were recorded during treadmill locomotion, and reaching and grasping. We explored whether the MLR's multi-unit activity is modulated during these movements. Among the rats, we found a consistent mean upregulation of the firing rate of 186.4±30.6% (mean ± SD) phase-locked with the onset of the hindlimb swing phase during locomotion. Across subjects and recording channels, this modulation shows different limb laterality preferences. Moreover, the peak firing rate of some channels significantly ($p<0.05$) encodes for walking speed. Besides locomotion, the MLR activity revealed regulation patterns during the movement of reaching and grasping, for both the ipsi- and contralateral forelimb. Specifically, a mean increase in firing rate of 130.5±27.5% in specific sub-phases compared to baseline activity was observed, for different recorded neurons, at the early stage of reaching, at grasping, and at pellet retrieving, respectively. Our results demonstrate how the MLR activity oversees distinct phases of locomotion, emphasizing its encoding of locomotor speed and bilateral limb control. Moreover, we show proof of MLR involvement during specific phases of discrete and skilled forelimb movements. The highlighted aspects of laterality control, phase-locked modulation, and skilled movements are crucial elements for motor BCI, thereby legitimating the exploration of the MLR as a novel target for such technologies.

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Poster

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Program #/Poster #: PSTR029.21/H9

Topic: E.05. Brain-Machine Interface

Support: NIH R01NS123663
Chen Neuroscience Institute
HHMI

Title: Neural representation of hand and foot action in intraparietal cortex of non-human primate

Authors: *L. SHE, S. LEE, M. G. SHAPIRO, D. A. WAGENAAR, R. A. ANDERSEN;
Caltech, Pasadena, CA

Abstract: The cortex within the intraparietal sulcus (IPS) in non-human primates (NHPs) is a brain region involved in planning eye movements and hand actions. Recent studies have shown that the homologue of anterior IPS in humans had broader roles, encoding the action of other body parts, observed actions and action verbs, and objects in allocentric coordinates. To understand the neural representation of IPS at both mesoscopic and single-neuron scale, we first performed functional ultrasound (fUS) imaging while the monkey performed a visually guided action task. Contrasting hand reach vs. grasp, we revealed that the parietal reach region (PRR) in the medial IPS showed much stronger activation during hand reach than grasp, consistent with the existing literature using single neuron recordings. We also demonstrated that both hand action type (reach vs. grasp) and target location could be decoded from single trial fUS signals in posterior IPS. However, the anterior intraparietal area (AIP) in anterior IPS, which was known to represent hand grasping, showed similar activation pattern for hand reach, grasping or foot grasping, suggesting a more abstract representation. Electrophysiological recording of AIP using high density probes (Neuropixels) confirmed that hand or foot actions were decodable at the single neuron level and the hand action related variables (hand action type, and target locations) were represented as well. This study provides evidence of a broader role for AIP and will help in developing less-invasive brain-machine interfaces using fUS imaging.

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Poster

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Topic: E.05. Brain-Machine Interface

Support: T&C Chen Brain-machine Interface Center, Caltech.

Title: Functional ultrasound neuroimaging through a human cranial window for decoding of movement effector somatotopy in primary motor cortex

Authors: *L. J. LIN[1,6], T. CALLIER[2], C. Y. LIU[2,7,8,9], M. G. SHAPIRO[3,4,10], R. A. ANDERSEN[2,5];
[2]Div. of Biol. and Biol. Engin., [3]Div. of Chem. & Chem. Engin., [4]Andrew and Peggy Cherng

Dept. of Med. Engin., [5]Tianqiao & Chrissy Chen Brain-machine Interface Ctr., [1]Caltech, Pasadena, CA; [7]Dept. of Neurolog. Surgery, [8]USC Neurorestoration Ctr., [6]Keck Sch. of Med. of USC, Los Angeles, CA; [9]Rancho Los Amigos Natl. Rehabil. Ctr., Downey, CA; [10]Howard Hughes Med. Inst., Pasadena, CA

Abstract: Brain machine interfaces (BMIs) can help patients with disabilities achieve greater independence by using their thoughts to control assistive devices. However, they commonly require highly invasive brain surgery for electrode implantation while conventional non-invasive imaging techniques like fMRI and EEG lack sufficient spatial resolution for high-bandwidth BMI use. Functional ultrasound (fUS) is a novel neuroimaging technique that balances these tradeoffs and can image from outside the dura with high sensitivity, high spatial resolution, and large field of view, demonstrating potential for use in less invasive BMIs. Prior work demonstrated that fUS can be used to decode movement intention in non-human primates and task state through a polymeric acoustic skull window in a human patient - the first steps toward enabling a minimally invasive fUS BMI. In this study, we show that fUS can further be used to decode motor effector information from primary motor cortex in a human participant with an acoustic window implant, demonstrating the growing applications of fUS for BMIs. Experiments were performed on a human participant who had previously undergone a hemicraniectomy procedure and polymeric skull reconstruction including an acoustic window. The participant was asked to perform block and single-trial memory-guided movement tasks using several different effectors while we acquired fUS data from the left primary motor cortex (M1). Using fUS, we identified somatotopic mapping of effectors in M1 during block tasks in which finger and wrist movements elicited more medial task-correlated activity and nose and mouth associated movements elicited more lateral task-correlated activity, matching canonical somatotopic mapping of M1. We then successfully used fUS to both identify significant task-correlated brain-regions, decode contralateral vs. ipsilateral movement, and decode movement effector at above-chance classification accuracy across different effectors in single-trial experiments. This work demonstrates that fUS could be used to decode movement effector information in a human subject with an acoustic window implant and presents significant progress in the development of a fUS-based BMI for decoding higher-level functions in humans. This highlights the potential of fUS as a minimally invasive alternative for BMIs in the future.

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Poster

PSTR029: Advances in Brain Computer Interfaces

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.23/H11

Topic: E.05. Brain-Machine Interface

Support: DOD Restoring Warfighters with Neuromusculoskeletal Injuries Research Award (RESTORE) W81XWH-21-1-0138

Title: Real-time decoding of distal and proximal arm muscle activity in object manipulation task

Authors: *S. BAHDASARIANTS[1], S. YAKOVENKO[2];
[1]West Virginia Univ., Morgantown, WV; [2]Human Performance, West Virginia Univ., Morgantown, WV

Abstract: Peripheral neuropathies commonly weaken or paralyze distal arm muscles, reducing dexterity in manipulation tasks. In brachial plexus injuries, individuals often retain control over proximal arm muscles, which can be exploited to inform distal muscle functional electrical stimulation. Particularly, behavior-specific coordination of proximal and distal muscles can be expressed as a set of stereotypical dynamic templates with invariable phase dependence. These templates can be recorded in healthy subjects and then used as behavior-specific proximal-to-distal activity decoders for individuals with impaired distal limb function. Here, we have developed a decoder that aligns real-time proximal muscle activity with its stereotypical template to infer movement phase and, consequently, the corresponding distal muscle activity. We tested the decoding in a task analogous to the Box and Block Test—a standardized assessment of manual dexterity where seated subjects transfer blocks across a partition. Surface electromyography was collected from seven proximal muscles (deltoids, biceps, triceps) and seven distal muscles (wrist and finger flexors and extensors, including brachioradialis), and contact forces were measured using force sensors attached to a block. The movement template was expressed as a spatiotemporal sequence of muscle activations, normalized in time and magnitude. Real-time proximal muscle activity was cross-correlated with the activity template to determine the current movement phase. Sensitivity analysis was used to optimize the algorithm's performance—peak computation speed and accuracy—for the following parameters: template resolution, template search window size, and current activity period. Template resolution ranged from 10 to 1000 samples representing the full phase; template search window size as well as current activity period ranged from 1 sample to 1000 samples. The best achieved performance had average phase error of ±9.7% and average amplitude error of ±15.0%. These initial findings support the development a population-based decoder to restore distal limb muscle functions via functional electrical stimulation for individuals with peripheral neuropathies.

Disclosures: S. Bahdasariants: None. **S. Yakovenko:** None.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.01/H12

Topic: E.05. Brain-Machine Interface

Support: UH3NS114439 (NINDS)
U01DC016686 (NIDCD)

Title: A self-paced silent speech BCI for home device control

Authors: *S. LUO[1], M. ANGRICK[1], C. COOGAN[1], D. CANDREA[1], K. WYSE-SOOKOO[1], A. SCHIPPERS[2], G. W. MILSAP[3], D. TIPPETT[1], N. J. MARAGAKIS[1], M. VANSTEENSEL[2], F. TENORE[3], M. S. FIFER[3], N. F. RAMSEY[2], N. E. CRONE[1];
[1]Johns Hopkins Univ., Baltimore, MD; [2]UMC Utrecht Brain Ctr., Utrecht, Netherlands; [3]Johns Hopkins Univ. Applied Physics Lab., Laurel, MD

Abstract: Brain-computer interfaces (BCIs) can potentially give people with paralysis the freedom to interact with smart devices in their homes. Many BCI applications have hitherto been constrained by the requirement that BCI commands be issued in response to visual or auditory cues (synchronous decoding). Uncued, asynchronous decoding is especially challenging for silent attempted speech. Here, we investigate whether silent attempted speech could be accurately detected and decoded to support device control without the need for these cues. We show that a clinical-trial participant with impaired speech and upper limb strength due to ALS used a chronically implanted electrocorticographic (ECoG) BCI succeed in controlling smart devices using silently attempted speech commands, without the need for cues or a visual display. These results demonstrate that silently attempted speech can be reliably decoded without exogenous timing cues, supporting the clinical viability of BCI-supported device control at home.

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Poster

PSTR030: Advances in Speech Prostheses

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Program #/Poster #: PSTR030.02/H13

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01-DC019498
NIH Grant UG3-NS120172

Title: Cross-patient speech decoding from preserved latent representations of speech production

Authors: *Z. SPALDING[1], S. DURAIVEL[1], S. RAHIMPOUR[2,3], C. WANG[1], K. BARTH[1], C. SCHMITZ[1], S. LAD[4], D. G. SOUTHWELL[4,5,6], J. VIVENTI[1,3,5,6], G. B. COGAN[4,7,8,6,9];
[1]Biomed. Engin., Duke Univ., Durham, NC; [2]Neurosurg., Univ. of Utah, Salt Lake City, UT; [3]Neurosurgery, Duke School of Medicine, Durham, NC; [4]Neurosurg., Duke Sch. of Med., Durham, NC; [5]Neurobiology, Duke School of Medicine, Durham, NC; [6]Duke Comprehensive Epilepsy Center, Duke University, Durham, NC; [7]Neurology, Duke School of Medicine, Durham, NC; [8]Biomedical Engineering, Duke University, Durham, NC; [9]Center for Cognitive Neuroscience, Duke University, Durham, NC

Abstract: Brain-computer interfaces (BCIs) show promise for restoring verbal communication to individuals with an inability to speak due to neurodegenerative disorders by using machine learning to decode words in real-time from neural signals. However, state-of-the-art speech BCIs are limited by long training times because they employ complex and patient-specific decoding models that demand weeks of data collection from a single patient for effective training. Recent work has shown that dynamical activity in cortical neural signals is preserved across patients when performing simple reaching tasks. We hypothesize that these neural dynamics are also preserved during complex motor tasks like speech production. This shared representation suggests that smaller datasets pooled across multiple patients could be used to train speech BCIs, reducing the quantity of individual patient data needed and saving training time. To investigate this, we placed high-density micro-electrocorticographic (µECoG) arrays over the sensorimotor cortex (SMC) of intraoperative patients instructed to perform a speech repetition task. We extracted time-varying high-gamma power (HG: 70-150 Hz) from recorded cortical signals during the patients' responses. We constructed latent feature spaces by decomposing HG dynamics with principal component analysis and subsequently aligned these spaces across patients to a common neural latent space using canonical correlation analysis (CCA). Preliminary results suggest that HG power is preserved in the SMC across multiple patients, as CCA successfully finds affine transformations of patients' latent dynamics that improve cross-patient correlations. To investigate the speech content encoded in these preserved dynamics, we trained support vector machine decoding models to predict the constituent phonemes of patients' responses. Decoding models predicted phonemes with higher accuracy when trained on cross-patient data aligned to a common latent space (41.4 ± 2.1%, chance: 11.1%) than when trained on patient-specific data (33.1 ± 5.3% chance: 11.1%). Further, this alignment technique allowed models to predict phonemes with accuracies well above chance on data from patients they had not been trained on (36.0 ± 5.9%, chance: 11.1%). These results suggest that there is a preserved neural representation of speech production across patients which can enable decoding models to train from cross-patient data. The next generation of speech BCIs can use this preserved neural representation to be trained more quickly from multiple patients and learn a robust, cross-patient representation of speech production.

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Poster

PSTR030: Advances in Speech Prostheses

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Topic: E.05. Brain-Machine Interface

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IDE Caution Statement: CAUTION: Investigational Device. Limited by Federal Law to Investigational Use.
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, or the Department of Veterans Affairs, or the United States Government.

Title: Stable Long-Term Neural Decoding with Minimum Adaptation

Authors: *T. K. PUN[1,2,3], J. JUDE[4,5], S. ALLCROFT[6,7], A. KAPITONAVA[4], S. H. BACH[8], L. R. HOCHBERG[6,7,4,5,3];
[1]Biomed. Engin. Grad. Program, Brown Univ., Providence, RI; [2]School of Engineering, Brown University, Providence, RI; [3]Carney Institute for Brain Science, Brown University, Providence, RI; [4]Ctr. for Neurotechnology and Neurorecovery, Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [5]Dept. of Neurol., Harvard Med. Sch., Boston, MA; [6]Sch. of Engin., Brown Univ., Providence, RI; [7]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Dept. of VA Med. Ctr., Providence, RI; [8]Dept. of Computer Sci., Brown Univ., Providence, RI

Abstract: Intracortical brain-computer interfaces (iBCIs) have enabled people with tetraplegia to control external devices via decoding movement intentions from neural recordings. iBCI is a practical technology for restoring communication through rapid point-and-click cursor control for applications such as typing, web browsing, and navigating apps on a tablet. However, current iBCI systems require frequent decoder re-calibration due to instability in neural recordings. Biological and technological instabilities could interfere with neural control performance when a previously trained decoder no longer describes the relationship between neural activity recordings and movement intention as this relationship can vary over time. Rather than explicitly re-calibrating the decoder, a better option is to develop an continuously adaptive decoder that is robust against within-day instability, but also converges to be more stable and maintain high performance as more training data become available.
We propose to develop a decoder with quick adaptation for practical everyday use and leverage available historical data of neural control. We applied a meta-learning training paradigm to mitigate the effect of distribution shift across days. We hypothesize that there is a stable neural embedding space governing consistent low-dimensional behaviors. To parameterize this space, each new session day is treated as a new task, and we train the model episodically sampled from these days. This method finds a lower-dimensional embedding onto which subsequent days of neural data can be projected. Since only a few time steps are required to build this representation under a few-shot learning setting, we can use this manifold representation for each subsequent day without needing to calibrate a whole new decoder. We tested the decoder on simulated neural data with added nonstationarity and previously collected longitudinal data from a participant with tetraplegia enrolled in the BrainGate2 clinical trial. The participant controlled a 2D computer cursor to perform a center-out-and-back task for 15 sessions spanned across 142 days using a fixed decoder. We showed in offline that this training procedure produces an ensemble decoder capable of high-performance cursor control with minimum data needed for same-day adaptation.

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Hochberg: F. Consulting Fees (e.g., advisory boards); The MGH Translational Research Center has a clinical research support agreement with Neuralink, Synchron, Reach Neuro, and Axoft for which L.R.H. provides consultative input., LRH is a co-investigator on an NIH SBIR grant with Paradromics, and is a non-compensated member of the Board of Directors of a nonprofit assistive communication device technology foundation, (Speak Your Mind Foundation). Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC), charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort..

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.04/H15

Topic: E.05. Brain-Machine Interface

Support: DOD CDMRP ALS Pilot Clinical Trial Award (AL220043), Searle Scholars Program, Career Award at the Scientific Interface from the Burroughs Wellcome Fund to Stavisky

Title: Decoding attempted speech amplitude from intracortical arrays in precentral gyrus

Authors: *A. SRINIVASAN[1], M. WAIRAGKAR[2], C. IACOBACCI[2], N. S. CARD[2], X. HOU[3], T. SINGER-CLARK[1], L. R. HOCHBERG[4], D. M. BRANDMAN[2], S. D. STAVISKY[2];
[1]Biomed. Engin., [2]Dept. of Neurolog. Surgery, [3]Computer Sci., Univ. of California, Davis, Davis, CA; [4]Brown Univ., Providence, RI

Abstract: Speech brain-computer interfaces (BCIs) can restore communication in people with severe speech impairment from neurodegenerative disorders like ALS, or stroke. Previous work has shown that BCIs can decode attempted speech into text and audio. Audio synthesized by speech BCIs can also be personalized to sound like an individual's pre-injury voice. However, computer synthesized voices typically do not capture paralinguistic components of speech which conveys emotional context. In this work, we focus on one paralinguistic speech component: amplitude, and report a neural decoder that can predict attempted speech amplitude from intracortical activity in the precentral gyrus.
We recorded intracortical signals from BrainGate2 clinical trial participant 'T15', a man in his 40s with ALS and severe dysarthria, using four 64-electrode Utah arrays chronically implanted in the left ventral precentral gyrus. Neural activity was recorded as the participant attempted to speak six unique words at four different speech amplitudes: silent, whisper, normal, and loud. In the neural activity surrounding attempted speech onset, 62% of the variance was explained by the top 3 principal components (PCs). The four attempted speech amplitudes were linearly separable in the top-3 PC subspace. Further, this amplitude separation was largely orthogonal to the organization of the attempted words in the same PC subspace. This suggests that motor

cortical correlates of attempted speech amplitude may be encoded independently of the phonetic content of the speech. Finally, a logistic regression classifier achieved 91.95% cross-validated classification accuracy in predicting attempted speech amplitude (chance = ~25%). The same model classified upcoming speech amplitude with 70% accuracy using neural activity from 200ms before speech onset.
These findings provide preliminary descriptions for speech amplitude encoding in ensemble spiking activity of cortical areas 4, 6v, and 55bs. These signals may be useful for adding amplitude-modulation capabilities to intracortical speech neuroprostheses.

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Poster

PSTR030: Advances in Speech Prostheses

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Topic: E.05. Brain-Machine Interface

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NIH grant EB028171
U01NS123101
NIH-NIDCD (1U01DC019430)

Title: An RNN Encoding Model for Understanding Continuous Speech Production in Motor Cortex

Authors: *C. FAN[1], B. MESCHEDE-KRASA[2,3], E. KUNZ[4,5], F. KAMDAR[6], N. S. CARD[7], M. WAIRAGKAR[7], C. IACOBACCI[7], L. R. HOCHBERG[8], D. M. BRANDMAN[9], S. D. STAVISKY[7], S. DRUCKMANN[10], J. M. HENDERSON[6], F. R. WILLETT[6];
[1]Stanford Univ., Palo Alto, CA; [2]Wu Tsai Neurosciences Inst., Stanford Univ., Palo Alto, CA; [3]Neurobiology, Stanford University, Palo Alto, CA; [4]Electrical Engin., Stanford Univ., Palo Alto, CA; [5]Wu Tsai Neurosciences Institute, Stanford University, Palo Alto, CA; [6]Neurosurg., Stanford Univ., Palo Alto, CA; [7]Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [8]Sch. of Engin., Brown Univ., Providence, RI; [9]Neurolog. Surgery, UC Davis Hlth., Sacramento, CA; [10]Neurobio., Stanford Univ., Palo Alto, CA

Abstract: Recently, we showed that intracortical recordings from the ventral precentral gyrus (vPCG) can be used to decode attempted speech in real-time at high accuracy [citations]. These recordings present a unique opportunity to understand the neural coding of continuous speech production. However, aligning neural activity to speech behavior requires precise timing of when phonemes are articulated. Our research participants cannot speak intelligibly due to amyotrophic lateral sclerosis (ALS), leaving us no reliable phoneme timing information. Additionally, each sentence spoken is unique, making it impossible to eliminate trial-to-trial variability in neural spiking activity by averaging multiple repetitions of the same condition.
To provide a more flexible framework for understanding these data, we developed a recurrent neural network (RNN) encoding model that can accurately predict the neural firing rates and phoneme timings resulting from any given phoneme sequence. This model leverages large amounts of data across many recording sessions to model how vPCG represents sequences of phonemes, allowing us to investigate the neural mechanisms underlying speech production by interrogating the model. We trained the model using neural data from two participants in the BrainGate2 clinical trial: T12, who has anarthria from ALS, and T15, who has dysarthria from ALS.
We used neural data (14.1 hours for T12, 12.8 hours for T15) of speaking English sentences to train the encoding model. The trained model can generate neural activity that is highly correlated with the real neural data (pearson r: 0.80 for T12, 0.85 for T15) on novel English sentences, showing it can accurately model vPCG activity. We then compare the model-generated neural activity on pairs of phoneme sequences, words, and sentences that differ only at one phonemic position. The results show that vPCG can encode multiple phonemes simultaneously (up to 8 past and future phonemes) within a word, but not across word boundaries. The future phonemes are encoded more strongly than the past ones. This suggests that vPCG plays a higher role in the hierarchy of speech production than simply generating the immediately upcoming articulatory

movements.
In conclusion, our study presents a novel approach to understanding the neural coding of continuous speech production. By using an encoding model, we show that vPCG encodes long sequences of past and future phonemes at a single moment in time. We believe that this method represents a unique data-driven approach to interpreting the neural coding of unstructured behavior, allowing many hypotheses to be tested in a quick and robust manner.

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Poster

PSTR030: Advances in Speech Prostheses

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Topic: E.05. Brain-Machine Interface

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The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, or the Department of Veterans Affairs or the United States Government.
CAUTION: Investigational Device

Title: Inferring Dynamics in Neural Recordings using LFADS with Per-trial Contextual Bias

Authors: *N. SHAH[1], B. MESCHEDE-KRASA[7], E. KUNZ[2], F. KAMDAR[3], D. AVANSINO[4], L. R. HOCHBERG[8], J. M. HENDERSON[5], D. SUSSILLO[6];
[1]Stanford Univ., Palo Alto, CA; [2]Electrical Engin., Stanford Univ., San Francisco, CA; [3]Stanford Univ., Moutnain View, CA; [4]Electrical Engineering, Neurosurg., Stanford Univ., San Mateo, CA; [5]Dept Neurosurgy, R 227, Stanford Univ., Stanford, CA; [6]Stanford Univ., Portola Valley, CA; [7]Stanford Univ. Neurosci. Phd Program, Palo Alto, CA; [8]Brown Univ., Providence, RI

Abstract: Interpreting neural ensemble dynamics from recorded activity is challenging. Linear models are easier to understand but can be inaccurate, while complex, non-linear models are more accurate but harder to interpret. Our "contextual LFADS" method models neural dynamics using a recurrent neural network (RNN) generator modulated by a learned per-trial constant bias. This method is based on the assumption that neural activity across similar conditions is related by simple changes in shared nonlinear dynamics (and that time-varying inputs do not play a role).
To illustrate the method, consider a collection of neural activity trials that correspond to oscillating pendulums of different lengths & masses. Under simplifying assumptions, modeling the dynamics of a single pendulum requires a single fixed point around which the pendulum's dynamics take place. So modeling a family of pendulums with differing lengths and masses with a single autonomous dynamical system requires a multistable system with a two-dimensional manifold of fixed points—one dimension for length and the other for mass. The initial condition of dynamics then not only must determine the initial position & velocity of the pendulum but also the fixed point with the best matching pendulum dynamics. Instead, a per-trial (pendulum) bias permits the reconfiguration of a single fixed point & dynamics around it to match different pendulums, simplifying the role of the initial condition to only represent initial pendulum velocity & position while also simplifying the task of interpreting the dynamics.
Contextual LFADS was applied to intracortical recordings from two human research participants (enrolled in the BrainGate2 safety clinical trial) as they attempted simultaneous movements of two finger groups or speaking single-syllable words with all pairwise combinations of three consonants. For both tasks, a low-dimensional per-trial bias successfully adapted autonomous RNN dynamics to produce the observed neural activity across conditions. The per-trial bias reflected the combinatorial structure of movements, altering a single fixed point and dynamics around it to capture changes in neural dynamics. Further, specific dimensions of the per-trial bias corresponded to non-task-related variations, such as shifts in mean channel activity (possibly due to recording nonstationarity) and changes in the speed of neural dynamics (possibly due to

behavioral variability). Projecting out these dimensions in per-trial bias reduced task-irrelevant variations & highlighted task-relevant components in neural activity.

Disclosures: **N. Shah:** None. **B. Meschede-Krasa:** None. **E. Kunz:** None. **F. Kamdar:** None. **D. Avansino:** None. **L.R. Hochberg:** A. Employment/Salary (full or part-time):; Robert J. and Nancy D. Carney Institute for Brain Science, Brown University, Providence, RI, USA, Center for Neurotechnology and Neurorecovery, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, VA RR&D Center for Neurorestoration and Neurotechnology, Rehabilitation R&D Service, Providence VA Medical Center, Providence, RI, USA. **J.M. Henderson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight Therapeutics. F. Consulting Fees (e.g., advisory boards); Neuralink, Paradromics. Other; Enspire DBS. **D. Sussillo:** A. Employment/Salary (full or part-time):; Meta Reality Labs.

Poster

PSTR030: Advances in Speech Prostheses

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Topic: E.05. Brain-Machine Interface

Support: NIH U01 DC019430
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Wu Tsai Neurosciences Institute at Stanford
Larry and Pamela Garlick

Title: Neural geometry of speech preparation in ventral premotor cortex

Authors: *B. MESCHEDE-KRASA[1], E. KUNZ[2], F. KAMDAR[3], N. CARD[6], M. WAIRAGKAR[7], C. IACOBACCI[8], S. R. NASON-TOMASZEWSKI[10], P. BECHEFSKY[11], L. R. HOCHBERG[12], D. BRANDMAN[13], S. D. STAVISKY[9], C. PANDARINATH[14], J. M. HENDERSON[4], S. DRUCKMANN[5];
[1]Stanford Univ. Neurosci. Phd Program, Palo Alto, CA; [2]Electrical Engin., Stanford Univ., San Francisco, CA; [3]Stanford Univ., Moutnain View, CA; [4]Dept Neurosurgy, R 227, [5]Stanford Univ., Stanford, CA; [6]Bioengineering, [7]Dept. of Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [8]Univ. of California, Davis, Pacifica, CA; [9]Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [10]Biomed. Engin., Emory Univ., Atlanta, GA; [11]UCLA, Los Angeles, CA; [12]Brown Univ., Providence, RI; [13]Neurolog. Surgery, UC Davis Hlth., Sacramento, CA; [14]Biomed. Engin., Emory Univ. and GA Tech., Decatur, GA

Abstract: Recent speech decoding brain-computer interfaces have shown impressive performance by predicting sequences of phonemes from ventral premotor cortex (area 6v)[1, 2]. However, the neural representations underlying the preparation and production of speech in these

areas remains poorly understood. The GODIVA model [3] predicts that ventral premotor cortex, including parts of area 6v, encodes a speech sound map which serves as a high level representation of sequences of speech sounds. Here we provide empirical evidence that 6v encodes whole sequences of phonemes before speech onset using neural representations that are shared across phoneme positions and task epochs (cue perception, preparation, and execution), consistent with 6v playing a higher level role in speech production that goes beyond feedback control of the speech articulators. Microelectrode arrays were placed in inferior 6v in three Braingate2 participants. In an instructed delay task, participants were cued with audio recordings of nonsense words composed of balanced sequences of three consonants separated by a repeated vowel. An example sequence of K-N-T was cued with the ARPABET phoneme sequence K-AH-N-AH-T. After a delay period, participants attempted to reproduce the cue. LDA models were fit to predict consonant phonemes individually for each position from delay period neural activity. All 3 phoneme positions were reliably decoded (classifier AUROCs consonant 1: 0.98, consonant 2: 0.89, consonant 3: 0.97) indicating that 6v can simultaneously encode phonemes in all positions. Models were then used to predict phonemes outside of the fitted position to assess similarity in phoneme encoding across position. Decoders fit between future consonants (positions 2 and 3) could generalize across context. Projecting held out trials into LDA coding dimensions revealed a shared neural geometry for future phoneme encoding. Next we fit decoders to each of 3 contexts (cue listening, delay, and execution) and found that decoders could generalize across context, revealing a representation of speech sounds not strictly limited to motoric preparation and execution of speech. These results demonstrate that in the speech planning hierarchy, area 6v encodes a generalized preparatory representation of sequences of speech sounds.

[1] Willett, F.R., Kunz, E.M., Fan, C. et al. A high-performance speech neuroprosthesis. Nature (2023).
[2] Card, N.S. et al. An accurate and rapidly calibrating neuroprosthesis. Medrxiv (2023).
[3] Bohland, JW., Bullock, D., & Guenther, F. H. (2010). Neural representations and mechanisms for the performance of simple speech sequences. Journal of cognitive neuroscience.

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Fees (e.g., advisory boards); Chethan Pandarinath is a consultant for Meta (Reality Labs). **J.M. Henderson:** F. Consulting Fees (e.g., advisory boards); Jaimie M. Henderson is a consultant for Neuralink Corp, serves on the Medical Advisory Board of Enspire DBS and is a shareholder in Maplight Therapeutics, He is also an inventor on intellectual property licensed by Stanford University to Blackrock Neurotech and Neuralink Corp;. **S. Druckmann:** F. Consulting Fees (e.g., advisory boards); Druckmann is a consultant for Ctrl labs.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.08/H19

Topic: E.05. Brain-Machine Interface

Support: Ketterer-Vorwald Neurosciences Interdisciplinary Graduate Fellowship

Title: Representation of verbal thought in motor cortex and implications for speech neuroprostheses

Authors: *E. M. KUNZ[1], B. MESCHEDE-KRASA[2], F. KAMDAR[3], S. R. NASON-TOMASZEWSKI[4], N. CARD[5], B. JACQUES[6], P. BECHEFSKY[7], N. HAHN[8], C. IACOBACCI[9], L. R. HOCHBERG[10], D. BRANDMAN[11], S. D. STAVISKY[12], N. AU YONG[7], C. PANDARINATH[13], S. DRUCKMANN[14], J. M. HENDERSON[15], F. R. WILLETT[16]; [1]Stanford Univ., San Francisco, CA; [2]Stanford Univ. Neurosci. Phd Program, Palo Alto, CA; [3]Stanford Univ., Moutnain View, CA; [4]Biomed. Engin., Emory Univ., Atlanta, GA; [5]Bioengineering, Univ. of California, Davis, Davis, CA; [6]Emory Univ., Decatur, GA; [7]Emory Univ., Atlanta, GA; [8]Neurosurg., Stanford Univ., Mountain View, CA; [9]Univ. of California, Davis, Pacifica, CA; [10]Brown Univ., Providence, RI; [11]Neurolog. Surgery, UC Davis Hlth., Sacramento, CA; [12]Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [13]Biomed. Engin., Emory Univ. and GA Technol., Decatur, GA; [14]Stanford Univ., Stanford, CA; [15]Dept Neurosurgy, R 227, Stanford Univ., Stanford, CA; [16]Neurosurg., Stanford Univ. / HHMI, Stanford, CA

Abstract: Brain-Computer Interfaces (BCIs) have recently demonstrated a viable path forward toward restoring speech to people who have lost the ability due to paralysis. Increased electrode count and optimized decoding algorithms have yielded a level of Signal-to-Noise-Ratio (SNR) and stability necessary for long-term use of a conversational open-ended speech BCI. However, as the performance of these intracortical systems has increased rapidly in decoding speech, so too has concern regarding their potential to decode private verbal thought.
In three research participants, each with microelectrode arrays placed along the precentral gyrus of the motor cortex, we studied different types of verbal behavior including: attempted vocalized speech, mimed speech, listening to speech, silently reading text, and three types of auditory or motor imagery of speech ("inner speech."), We found that all behaviors, including the three inner speech conditions, showed distinct representations of individual words, with overt movement

conditions generally showing the strongest modulation, as expected. The strongest modulation for perceived and inner speech was found in Area 55b and the inferior region of Area 6v (as defined by the Human Connectome Project cortical parcellations). Notably, a simple classifier of 7 words could distinguish the neural signals during listening and inner speech above chance in all participants, with up to 94% accuracy for listening and 71% for inner speech. Additionally, we found these word-level representations were largely shared across perceived, inner and produced speech, differing primarily in relative strength of modulation from rest. We also demonstrate the first online speech neuroprosthesis for decoding continuous inner speech from three individuals with dysarthria, achieving a word error rate as low as 14% for a 50 word vocabulary. All participants found inner speech easier, more comfortable, and aesthetically preferable as compared to actually attempting to vocalize, as is the typical paradigm for state-of-the-art speech neuroprostheses.
Finally, to understand whether verbal thought might be decodable when it occurs naturally, we ran a follow-up research session that elicited the natural use of inner speech as a memory aid in a non-speech task (drawing symbolically-cued sequences). We found that the content of the inner speech in this task was discernible using a decoder trained on attempted vocalized speech. This brings to light some important questions regarding decoding intention and privacy that future design of speech neuroprostheses must take into account.

Disclosures: **E.M. Kunz:** None. **B. Meschede-Krasa:** None. **F. Kamdar:** None. **S.R. Nason-Tomaszewski:** None. **N. Card:** None. **B. Jacques:** None. **P. bechefsky:** None. **N. Hahn:** None. **C. Iacobacci:** None. **L.R. Hochberg:** 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 SBIR with Paradromics. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC. F. Consulting Fees (e.g., advisory boards); Neuralink, Synchron, Reach Neuro, Axoft, and Precision Neuro. **D. Brandman:** F. Consulting Fees (e.g., advisory boards); Paradromics Inc. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp.. Other; wispr.ai. **N. Au Yong:** None. **C. Pandarinath:** None. **S. Druckmann:** None. **J.M. Henderson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); shareholder in Maplight Therapeutics, an inventor on intellectual property licensed by Stanford University to Blackrock Neurotech and Neuralink Corp. F. Consulting Fees (e.g., advisory boards); consultant for Neuralink Corp, serves on the Medical Advisory Board of Enspire DBS. **F.R. Willett:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); an inventor on intellectual property licensed by Stanford University to Blackrock Neurotech and Neuralink Corp.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: E.05. Brain-Machine Interface

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CAUTION: Investigational Device. Limited by Federal Law to Investigational Use

Title: Hierarchical representations of language in human cortex at the single neuron level

Authors: *H. LEVI-AHARONI[1,2], J. JUDE[1,2], S. ALLCROFT[3,5], A. ACOSTA[2], S. HARO[3], J. D. SIMERAL[6,3], L. HOCHBERG[7,3,2,1,4], D. B. RUBIN[2,1];
[1]Harvard Med. Sch., Boston, MA; [2]Ctr. for Neurotechnology and Neurorecovery, Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [3]Sch. of Engin., [4]Carney Inst. for Brain Sci., Brown Univ., Providence, RI; [5]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Dept. of VA Med. Ctr., Providence, RI; [6]Dept. of VA Med. Ctr., VA CfNN & Brown Univ. Sch. Eng., Providence, RI; [7]Dept. of VA Med. Ctr., VA RR&D Ctr. for Neurorestoration and Neurotechnology, Boston, MA

Abstract: Recent investigation into the representation of language production at the single-neuron level has revealed both a phonemic and syllabic encoding within language-processing areas of the dominant prefrontal cortex [1, 2]. Within an individual research participant, these representations contain sufficient information to control a phoneme-based intracortical brain-computer interface (iBCI) for decoding intended speech [3, 4]. However, it is unknown whether these cortical areas also encoded higher-level representations of language. In this work, we examine the cortical representation of linguistic information beyond the phoneme level (e.g., at the level of words, phrases, and sentences), and characterize how this hierarchical linguistic information is encoded in different cortical areas. This research was performed using datasets from two participants with ALS enrolled in the BrainGate clinical trial. One dataset is from research sessions conducted with an anarthric individual with six Utah arrays placed in the speech-related areas of motor cortex (in areas 6v, 55b and 6d); the other is from sessions conducted with a dysarthric individual with arrays in cortical areas 6v and 44 (Broca's area).We investigate the differential encoding of phonemes, words and sentences in these areas across the human cortex and in the single-channel neuronal activity within these areas. In order to characterize different levels of language production, we use a framework known as Brain-Score [5] to quantitatively evaluate the expressivity of each channel in terms of its activation similarity to layers of a deep language model (DLM). Our analysis shows higher similarity scores with lower levels of the DLM for motor area 6v compared to Broca's area, which shows higher

similarity scores with middle layers. We hypothesize that this scoring can be used to improve iBCI speech decoders by incorporating information from higher linguistic levels and by using different sets of neurons for the appropriate level being decoded, thereby making iBCI speech decoders more accurate and efficient.
1.Khanna, A. R. et al. Single-neuronal elements of speech production in humans. Nature 626, 603-610 (2024).2.Silva, A. B. et al. A Neurosurgical Functional Dissection of the Middle Precentral Gyrus during Speech Production. Journal of Neuroscience 9 Nov, 42 (45) 8416-8426 (2022).3.Willett, F.R. et al. A high-performance speech neuroprosthesis. Nature 620, 1031-1036 (2023). 4.Metzger, S.L. et al. A high-performance neuroprosthesis for speech decoding and avatar control. Nature 620, 1037-1046 (2023).5.Schrimpf M. et al. Integrative Benchmarking to Advance…, Neuron 108, 413-423 (2020).

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Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

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Topic: E.05. Brain-Machine Interface

Support: DP2 from the NIH Office of the Director and managed by NIDCD (1DP2DC021055); Searle Scholars Program; and a Career Award at the Scientific Interface from the Burroughs Wellcome Fund to Stavisky Stanford Wu Tsai Neurosciences Institute, HHMI, Simons Foundation and NIH-NIDCD (1U01DC019430) to Jaimie Henderson

Title: Characterizing language-related error signals with intracortical arrays in inferior frontal gyrus and ventral precentral gyrus

Authors: *X. HOU[1,2], C. IACOBACCI[3], N. S. CARD[3], M. WAIRAGKAR[3], T. SINGER-CLARK[4,2], F. R. WILLETT[5], E. M. KUNZ[6,7], C. FAN[8], F. KAMDAR[9], N. HAHN[9], L. R. HOCHBERG[10,11,12], J. M. HENDERSON[9,7], D. M. BRANDMAN[3], S. D. STAVISKY[3]; [1]Computer Sci., Univ. of California, Davis, Davis, CA; [2]Neurological Surgery, University of

California, Davis, Davis, CA; [3]Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [4]Biomed. Engin., Univ. of California, Davis, Davis, CA; [5]Howard Hughes Med. Inst. at Stanford Univ., Stanford, CA; [6]Electrical Engin., Stanford Univ., Stanford, CA; [7]Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA; [8]Computer Sci., Stanford Univ., Stanford, CA; [9]Neurosurg., Stanford Univ., Stanford, CA; [10]Sch. of Engin. and Carney Inst. for Brain Sci., Brown Univ., Providence, RI; [11]VA RR&D Center for Neurorestoration and Neurotechnology, VA Providence Healthcare, Providence, RI; [12]Center for Neurotechnology and Neurorecovery, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Abstract: Neural signals associated with task outcome errors reflect discrepancies between expected and actual outcomes. In the context of brain-computer interfaces for restoring communication, users will discern the difference between their attempted action and what the BCI does. This mismatch generates an error signal within the brain. Previous work with human participants has demonstrated the existence of error signals in dorsal precentral gyrus during BCI control of a computer cursor (Even-Chen 2017). Here, we characterize errors in speech from recordings in the ventral precentral gyrus (vPCG) and inferior frontal gyrus (IFG) during the use of a speech neuroprosthesis.

We analyzed data from two participants in the ongoing BrainGate2 clinical trial. Participant T12 is a 68-year old woman with ALS with severe dysarthria who has 2 chronic 64-microelectrode Utah arrays implanted in vPCG and 2 arrays in IFG. Participant T15 is a 45-year old man with ALS with severe dysarthria who has 4 arrays implanted in vPCG. In an instructed-delay paradigm, we recorded neural activity while participants attempted to speak a cue word, and then were presented with a second word on-screen shortly thereafter. The participants were asked to report if the second word was correct (i.e., matched the cue word) or incorrect. On some trials, the second word correctly matched the cue word. However, the task deliberately displayed 1 of 4 "incorrect" outputs on ~60% of trials. Incorrect output words could be a pseudoword, a homophone of the cue word, a minimal pair difference from the cue, or a synonym (e.g., for cue "son", incorrect words were "sen", "sun", "sin", "child"). We analyzed a time epoch from 200 ms before to 1000 ms after the second word display. We applied SVM classifiers to predict if a trial had incorrect feedback, as well as the type of the introduced error using a 50 ms sliding window of spike counts and spike band power. Finally, we evaluated the classifiers through a cross-validation method where two word sets were excluded to confirm generalizability.

Offline analyses demonstrated above-chance accuracies in classifying whether the second word was correct vs. incorrect, as well as the type of error in incorrect trials. For T12, the accuracy of classifying correctness was 90.1% (chance level at 50%) at 590 ms after the second word display when error type classification accuracy peaked at 67.3% (chance level at 25%). For T15, the accuracies were 75.1% and 53.1% respectively at 430 ms. These results indicate encoding of language-related differences between attempted and feedback words in the human IFG and vPCG and suggest an opportunity to further improve the performance of speech neuroprostheses.

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None. **E.M. Kunz:** None. **C. Fan:** None. **F. Kamdar:** None. **N. Hahn:** None. **L.R. Hochberg:** 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.; The MGH Translational Research Center has a clinical research support agreement with Neuralink, Synchron, Axoft, Precision Neuro, and Reach Neuro, for which Hochberg provides consultative input. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC), charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **J.M. Henderson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp., shareholder in Maplight Therapeutics. F. Consulting Fees (e.g., advisory boards); consultant for Neuralink Corp, serves on the Medical Advisory Board of Enspire DBS. **D.M. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); surgical consultant to Paradromics Inc. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp., patent applications related to speech BCI owned by the Regents of the University of California, was an advisor to wispr.ai and received equity.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: E.05. Brain-Machine Interface

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Department of Veterans Affairs Rehabilitation Research and Development Service A2295R
Emory Neuromodulation and Technology Innovation Center (ENTICe)

Title: A multifunctional speech and movement intracortical brain-computer interface for communication

Authors: *S. R. NASON-TOMASZEWSKI[1], B. G. JACQUES[1], Y. H. ALI[1], M. RIGOTTI-THOMPSON[1], A. L. PRITCHARD[1], P. H. BECHEFSKY[1], L. R. HOCHBERG[2,3,4,5], N. AU YONG[6,7,1], C. PANDARINATH[1,6];
[1]Wallace H. Coulter Dept. of Biomed. Engin., Emory Univ. and Georgia Inst. of Technol., Atlanta, GA; [2]Ctr. for Neurotechnology and Neurorecovery, Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [3]Carney Inst. for Brain Sci. and Sch. of Engin., Brown Univ., Providence, RI; [4]Dept. of Neurol., Harvard Med. Sch., Boston, MA; [5]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Deptartment of Veterans Affairs Med. Ctr., Providence, RI; [6]Dept. of Neurosurg., [7]Dept. of Cell Biol., Emory Univ., Atlanta, GA

Abstract: Brain-to-text brain-computer interfaces (BCIs) have recently enabled people with dysarthria to communicate at rates and accuracies comparable to able speakers. However, decoding accuracy is not 100%, requiring users to occasionally correct the predicted text, which can be tedious with a speech-only BCI. Here, we explore design constraints for multifunctional intracortical BCIs that combine rapid brain-to-text predictions (via attempted speaking) with cursor control for text correction (via intended arm/hand movements) to improve accuracy while maintaining rate of text entry. We recorded spiking activity from participant T16 (BrainGate2, ClinicalTrials.gov: NCT00912041), a 52 year old female with chronic tetraplegia and dysarthria due to a pontine stroke. We placed four 64-channel NeuroPort intracortical microelectrode arrays: two in hand knob (area 6d), one in speech-related ventral precentral gyrus (PCG; 6v), and one on the border of the premotor eye field and speech-related middle PCG (PEF/55b). T16 performed an instructed delay task that included speaking (SP) and movement phases (MP). During SP, T16 was asked to mouth one of four words ("bring," "help," "nurse," "where"), or no word was prompted. During MP, T16 attempted movements to one of four targets (up, down, left, right), or made no movement attempt. We assessed whether each array's modulation was behavior-specific via peri-stimulus time histograms (PSTHs) and cross-validated signal-to-noise ratios (cvSNRs; measures separability relative to "do nothing"; 0 means no separability). We also used support vector machines (SVMs) to classify words and movements to assess each array's specificity to its preferred behavior. 6v electrodes were strongly modulated during the SP (2.82 and 0.0164 cvSNR for mouthing and movement, respectively) and 6d electrodes were strongly modulated during the MP (1.74 and 0.345 cvSNR for movement and mouthing, respectively), both as expected. Perhaps surprisingly, PEF/55b electrodes were modulated for both the SP and MP (1.50 and 1.77 cvSNR, respectively). SVMs also classified each array's preferred behavior with high accuracy (6v 97.3%, 6d 89.5% correct; chance 20%) relative to its less-modulated behavior (6v 34.7%, 6d 28.3%). Importantly, SVMs also generalized to unseen word-movement pairs and predicted the correct word or movement per the array's preferred behavior (6v 97.7%, 6d 89.2%), suggesting modulation may not be heavily impacted by secondary behaviors. These results suggest speech- and movement-related neural activity relevant to a multifunctional intracortical BCI are relatively isolated even when both behaviors are performed consecutively.

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advisory boards); Neuralink, Synchron, Reach Neuro, Axoft, Precision Neuro. **N. Au Yong:** None. **C. Pandarinath:** F. Consulting Fees (e.g., advisory boards); Meta (Reality Labs).

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01NS121079

Title: Enhancing movement-related activity in neural reach representations via intracortical BCI decoder gain perturbations

Authors: *W. HOCKEIMER[1,2], B. DEKLEVA[1,2,3], N. G. KUNIGK[1,4,3], M. BONINGER[1,2,4], S. M. CHASE[5,6,7], J. L. COLLINGER[1,2,4,3,6];
[1]Rehab Neural Engin. Labs, Univ. of Pittsburgh, Pittsburgh, PA; [2]Physical Medicine and Rehabilitation, University of Pittsburgh, Pittsburgh, PA; [3]Center for the Neural Basis of Cognition, Pittsburgh, PA; [4]Bioengineering, University of Pittsburgh, Pittsburgh, PA; [5]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [6]Biomedical Engineering, Carnegie Mellon University, Pittsburgh, PA; [7]Neuroscience Institute, Carnegie Mellon University, Pittsburgh, PA

Abstract: Intracortical brain-computer interfaces (BCIs) allow individuals with paralysis to control external devices through a decoder that maps neural activity to kinematic commands. While BCIs for computer access can perform well, they do not yet replicate an able-bodied level of function. We posit that one means of improving control is to enhance the strength of movement-related information in the neural control signal. Data were collected from two male participants with tetraplegia who were enrolled in a clinical trial of a sensorimotor BCI. Participants completed a 2D center-out task in which they were instructed to reach to one of four quarter-circle radial targets as quickly as possible by controlling a computer cursor with their BCI. We evaluated whether they could exhibit strengthened movement-related neural activity decoded from motor cortex firing rates. Performance was quantified during a baseline evaluation block. The cursor gain, i.e. its speed, was then reduced during a perturbation block. We hypothesized that participants would adapt to the perturbation by commanding larger cursor velocities than they had used during the baseline evaluation, even though participants were instructed to move as fast as possible during all epochs. In both participants, the peak decoded velocity per trial was greater during perturbation compared to baseline (P2 3/4 days $p < 0.05$, P3 2/2 days $p < 0.05$, Mann-Whitney rank test within day). The ability to produce faster velocity commands implies that there was stronger movement-related neural activity generating those commands. The perturbation was removed, and performance was quantified in a ‘washout’ evaluation block. For both participants, the peak decoded velocity returned to the baseline level. We suspect that the participants returned to their normal range of velocities due to speed-accuracy tradeoffs. In conclusion, BCI gain manipulation applied significant performance

pressure that enabled participants to increase the strength of movement-related modulation beyond that previously observed during calibration or BCI performance. Future work will explore multi-day learning to test whether changes to the distribution of decoded velocities can persist beyond the perturbation period, which would improve movement-related activity in a lasting, and potentially generalizable, manner.

Disclosures: W. Hockeimer: None. **B. Dekleva:** None. **N.G. Kunigk:** None. **M. Boninger:** 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.; Blackrock Microsystems. **S.M. Chase:** None. **J.L. Collinger:** 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.; Blackrock Microsystems.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.13/H24

Topic: E.05. Brain-Machine Interface

Support: Dutch Science Foundation SGW-406-18-GO-086
Dutch Technology Foundation UGT7685
European Research Council ERC-Advanced 'iConnect' project, grant ADV 320708
National Institute on Deafness and Other Communication Disorders U01DC016686
National Institute of Neurological Disorders and Stroke UH3NS114439

Title: Auditory feedback influences accuracy of speech decoding: Implications for speech Brain-Computer Interface development for locked-in individuals

Authors: *A. SCHIPPERS[1], J. BEREZUTSKAYA[1], Z. V. FREUDENBURG[1], S. LUO[3], N. E. CRONE[4], M. VANSTEENSEL[2], N. F. RAMSEY[1];
[2]Neurol. and Neurosurg., [1]UMC Utrecht Brain Ctr., Utrecht, Netherlands; [3]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [4]Neurol., The Johns Hopkins Univ., Baltimore, MD

Abstract: Recent developments in the field of brain-computer interfaces (BCI) have demonstrated their potential to restore communication in individuals with locked-in syndrome (LIS). Modulations in high-frequency band (HFB) power in the sensorimotor cortex (SMC), generated by (attempted) speech, can be decoded into computerized speech. For the accurate production of speech by able-bodied people auditory feedback plays an important role, and altered or absent feedback has direct implications on speech behavior. Whereas individuals with

LIS can attempt to speak, they will not be able to produce auditory feedback. The question remains to what extent the absence of auditory feedback influences SMC brain activity patterns during attempted speech, and therefore speech decoding accuracy. Here, we investigated the effect of auditory feedback on SMC activity, and we compared speech decoding performance in the presence and absence of auditory feedback. Three epilepsy patients were subdurally implanted with high density electrocorticography (ECoG) grids over the left SMC. Participants completed two speech tasks, one in which they could hear themselves speak, and one in which pink noise was administered to mask their auditory feedback. In both tasks, participants were instructed to overtly produce a sequence of seven syllables. After preprocessing and the extraction of the HFB power (65 - 95 Hz) from the ECoG data, R2 analysis was used to determine which electrodes showed a significant increase in HFB power during speech compared to periods of rest. All participants showed widespread SMC engagement during both tasks. To test decodability of the produced sounds, a support vector machine classifier was applied to the data following a nested cross-validation approach. A leave-one-group-out approach was used, where one instance of each of seven unique syllables were left out as test data on every fold. Produced syllables were decoded with above-chance accuracies for all subjects, and ranged between 36% - 62%. A significant difference was found within each subject in the classification scores between the two tasks, where for all subjects lower accuracy was achieved in the task where no auditory feedback was perceived. The current study demonstrates that while above-chance decoding of syllable production can be achieved when auditory feedback is absent, the decoding accuracies are negatively affected when speakers cannot hear themselves. This implies that for individuals with LIS, optimal classification accuracy may be lower compared to abled individuals, and that for BCI users who can still speak, decoding performance may decline over time if their ability to vocalize decreases.

Disclosures: A. Schippers: A. Employment/Salary (full or part-time):; UMC Utrecht Brain Center. **J. Berezutskaya:** A. Employment/Salary (full or part-time):; UMC Utrecht Brain Center. **Z.V. Freudenburg:** A. Employment/Salary (full or part-time):; UMC Utrecht Brain Center. **S. Luo:** A. Employment/Salary (full or part-time):; The Johns Hopkins University. **N.E. Crone:** A. Employment/Salary (full or part-time):; The Johns Hopkins University. **M. Vansteensel:** A. Employment/Salary (full or part-time):; UMC Utrecht Brain Center. **N.F. Ramsey:** A. Employment/Salary (full or part-time):; UMC Utrecht Brain Center.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.14/H25

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N2864C, N9228C, A4820R, A2295R, B6453R, B6459L, A6779L, P1155R, A2827R, A3803R)
NIH NIDCD (R01DC009899), NIH NIDCD (U01DC017844), NIH

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Robert J. and Nancy D. Carney Institute for Brain Science, Brown University School of Engineering,Brown University Office of the Vice President for Research
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Title: Long term performance of intracortical microelectrode arrays for cursor control in 14 BrainGate participants

Authors: *N. HAHN[1], E. STEIN[2], J. D. SIMERAL[3,4,5], L. R. HOCHBERG[3,4,5,6,7], J. M. HENDERSON[1,8,9], F. WILLETT[1,10,8,11];
[1]Neurosurg., Stanford Univ., Stanford, CA; [2]Electrical Engin., Stanford Univ., Stanford, CA; [3]VA CfNN & Brown Univ. Sch. Eng., Providence, RI; [4]School of Engineering, Brown University, Providence, RI; [5]Carney Institute for Brain Science, Brown University, Providence, RI; [6]Center for Neurotechnology and Neurorecovery, Dept. of Neurology, Massachusetts General Hospital, Boston, MA; [7]Neurology, Harvard Medical School, Boston, MA; [8]Wu Tsai Neuro. Inst., Stanford, CA; [9]Bio-X Program, Stanford University, Stanford, CA; [10]Electrical Engineering, Stanford University, Stanford, CA; [11]HHMI at Stanford University, Stanford, CA

Abstract: Intracortical brain computer interfaces have enabled people with paralysis to control computer cursors, prosthetic limbs, and communicate via handwriting, speech, and typing. Understanding the longevity of intracortical microelectrode arrays is necessary to assess clinical viability and inform the next generation of recording technology. Peer-reviewed literature provides incidental evidence of the long-term viability of intracortical recording in humans. However, explicit multi-participant longevity evaluation in humans is rare and prior studies have examined data from only one or two individuals.
Between 2004 and 2020, one or two Utah microelectrode arrays (1.0 or 1.5mm) were placed in the hand knob area of motor cortex in 14 human participants as part of the BrainGate clinical trials. To evaluate array longevity, we calculated the number of electrodes that detected spiking activity (“spiking electrodes”) from 2,271 total experimental sessions. Spiking activity was

defined as a median threshold-crossing rate greater than 2 Hz when using a -4.5 RMS threshold. Total implant days ranged from 296 to 2780 days (7.6 years) with a mean of 1091 days (n=19 arrays). The mean spiking electrode yield was 34.26% across 19 arrays. The number of spiking electrodes decreased slightly throughout the recording duration, with a mean of -1.62 spiking electrodes every 6 months (median -0.79, std 11.02, n=19 arrays). There was large inter-subject variability; for example, participant T2's array experienced a steep decline over the first year, whereas participant T8's lateral array reached a maximum yield 875 days post implant. For many arrays, spiking electrode count appeared to fluctuate around the mean, with only a slight overall decline.

To evaluate array decoding performance, cursor control sessions were analyzed for 14 arrays from the 9 most recent participants. Offline linear decoder output within a 400ms window was decomposed into a signal component (pointing toward the target) and a noise component to calculate a decoding signal to noise ratio (dSNR). The mean dSNR was 1.78 (std 1.17, n=14 arrays) and ranged from 0.08 to 3.22. Overall changes in dSNR throughout the recording duration were minimal, with a mean delta of +0.01 every 6 months (std: 0.52, n=14). Participants with higher spiking electrode counts generally had higher dSNR (pearson r: 0.69, p value: 0.006), with some exceptions. Notably, participant T6 had a mean dSNR of 2.36 despite having a spiking electrode yield of only 7.89%.

Overall, these results show that Utah microelectrode arrays typically retain performance for long durations, but can vary widely in absolute performance level.

Disclosures: **N. Hahn:** None. **E. Stein:** None. **J.D. Simeral:** None. **L.R. Hochberg:** Other; The Center for Neurotechnology and Neurorecovery has clinical research support agreements with Neuralink, Synchron, Reach Neuro, Axoft, and Precision Neuro, for which LRH provides consultative input, MGH is a subcontractor on an NIH SBIR with Paradromics. Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC);, charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **J.M. Henderson:** Other; consultant for Neuralink Corp, serves on the Medical Advisory Board of Enspire DBS and is a shareholder in Maplight Therapeutics, He is also an inventor on intellectual property licensed by Stanford University to Blackrock Neurotech and Neuralink Corp. **F. Willett:** Other; is an inventor on intellectual property licensed by Stanford University to Blackrock Neurotech and Neuralink Corp.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.15/H26

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N2864C,A4820R, A2295R)
NIH NIDCD (U01DC017844, R01DC014034, U01DC019430,

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Brown University Provost's STEM Postdoctoral Fellowship to S. Haro
A.P. Giannini Postdoctoral Fellowship to N. Card
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CAUTION: Investigational Device. Limited by Federal Law to Investigational Use

Title: Tailoring the Use of a Chronically-Implanted Intracortical Speech Neuroprosthesis for a Person With Long-Standing Anarthria

Authors: *S. HARO[1], J. J. JUDE[2,3], A. J. ACOSTA[2], H. LEVI-AHARONI[2,3], S. ALLCROFT[1], N. S. CARD[4], M. WAIRAGKAR[4], D. M. BRANDMAN[5], S. D. STAVISKY[4], J. D. SIMERAL[6,7], L. R. HOCHBERG[1,8,3,9,10], D. B. RUBIN[11];
[1]Sch. of Engin., Brown Univ., Providence, RI; [2]Ctr. for Neurotechnology and Neurorecovery, Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [3]Harvard Medical School, Boston, MA; [4]Dept. of Neurolog. Surgery, Univ. of California Davis, Davis, CA; [5]Neurolog. Surgery, Univ. of California Davis, Davis, CA; [6]Ctr. for Neurorestoration and Neurotechnology (CfNN), Rehabil. R&D Service, DVA, Providence, RI; [7]School of Engineering, Brown University, Providence, MA; [8]Center for Neurotechnology and Neurorecovery, Department of Neurology, Massachusetts General Hospital, Boston, MA; [9]Center for Neurorestoration and Neurotechnology (CfNN), Rehabilitation R&D Service, Department of Veterans Affairs, Providence, RI; [10]Robert J. and Nancy D. Carney Institute for Brain Science Institute for Brain Science, Brown University, Providence, MA; [11]Neurol., Massachusetts Gen. Hosp., Boston, MA

Abstract: Intracortical brain-computer interfaces (iBCI) developed as part of the BrainGate clinical trial have demonstrated high-performance speech decoding for two participants with dysarthric speech due to ALS (Willett 2023, Card 2023 medRxiv). These two participants have intact respiration and varying degrees of control over speech articulators and vocalization. In the present study, we tailored the use of a similar speech neuroprosthesis for a 33 year-old BrainGate participant with anarthria and ventilator dependence due to advanced ALS. This participant, T17, has six Utah 64-microelectrode arrays placed in his left precentral gyrus (two each in areas 6v, 55b, and 6d/4). During initial sessions, phoneme decoding performance was significantly greater than chance but below the level of accuracy required to support closed-loop communication. Consequently, we undertook significant effort to optimize signal quality, both from a technical and participant-based perspective. Regarding our participant, we hypothesized that more intensive task-imagery, instruction, and practice would help boost decoding performance. Thus, we provided T17 with tailored instructions on phoneme-level articulation, larynx voicing activation, as well as the intentional syllabification of words, taking into account his ventilator-dependence and self-expressed difficulty with certain phonemic production tasks. Speaking exercises were embedded within task instructions. T17 performed isolated phoneme sweeps, orofacial movement sweeps, word sweeps using words from a standardized 50-word corpus, and minimal word pair exercises where pairs of words only differed by a single consonant or vowel.

Preliminary results include a 12.24% improvement in decoded isolated consonant accuracy from 39.58% to 51.82% using a forced-40-choice Gaussian Naive Bayes classifier (chance = 2.5%), with main effects of consonant place and session index ($p < 0.0005$, $p = 0.075$, respectively). In subsequent weeks, T17 received additional instructions and exercises designed at activating various aspects of speech that may be impacted by his anarthria and ventilator dependence. While we cannot rule out the impact of improvements to signal quality obtained through concurrent technical enhancements in the signal processing pipeline, we remain encouraged by our results demonstrating the potentially positive impact of tailored speech training interventions on decoding performance. Ongoing efforts focused on single-unit and population level analyses aim to quantify the precise impact of each of our interventions on signal information content.

Disclosures: **S. Haro:** None. **J.J. Jude:** None. **A.J. Acosta:** None. **H. Levi-Aharoni:** None. **S. Allcroft:** None. **N.S. Card:** None. **M. Wairagkar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. **D.M. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); surgical consultant to Paradromics Inc. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California, inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp. F. Consulting Fees (e.g., advisory boards); advisor to wispr.ai and received equity. **J.D. Simeral:** None. **L.R. Hochberg:** Other; The MGH Translational Research Center has a clinical research support agreement (CRSA) with Axoft, Neuralink, Neurobionics, Precision Neuro, Synchron, and Reach Neuro, for which LRH provides consultative input. LRH is a co-investigator on an NIH SBIR grant with Paradromics, and is a non-compensated member of the Board of Directors of a nonprofit assistive communication device technology foundation (Speak Your Mind Foundation), Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC); charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **D.B. Rubin:** None.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.16/H27

Topic: E.05. Brain-Machine Interface

Support: A.P. Giannini Postdoctoral Fellowship
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ALS Association Assistive Technology Grant (24-AT-732)

DP2 from the NIH Office of the Director and managed by NIDCD (1DP2DC021055)
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Searle Scholars Program
Career Award at the Scientific Interface from the Burroughs Wellcome Fund

Title: Evaluating the Usability of a Conversational Speech Neuroprosthesis for a Participant with ALS

Authors: *H. PERACHA[1], **C. IACOBACCI**[2], N. CARD[2], M. WAIRAGKAR[2], X. HOU[2], T. SINGER-CLARK[2], L. R. HOCHBERG[3], S. D. STAVISKY[2], D. BRANDMAN[4];
[1]Neuorological Surgery, [2]Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [3]Dept. of Neurol., Brown Univ., Providence, RI; [4]Neurolog. Surgery, UC Davis Hlth., Sacramento, CA

Abstract: Communication is paramount to our sense of agency as social creatures. Unfortunately, for the thousands of people living with dysarthria due to neurological diseases and disorders such as stroke and amyotrophic lateral sclerosis (ALS), communication can range from difficult to impossible. This can lead to increased rates of isolation, depression, and decreased quality of life. Although not commercially available yet, brain computer interfaces (BCIs) offer a promising path toward restoring fast and intuitive communication to people with dysarthria. As a part of the BrainGate2 clinical trial, we have previously demonstrated accurate speech decoding from neural activity into text on a screen using an intracortical BCI. This work aims to explore and evaluate the usability of this speech BCI for conversational speech decoding in a variety of contexts.
We recruited a 45 year old man with ALS (participant 'T15') to the BrainGate2 clinical trial and placed 4 microelectrode arrays into his ventral precentral gyrus (vPCG). These microelectrode arrays record his neural activity as he attempts to speak and decodes it into words that are displayed on a screen as text (Card et al. medRxiv 2023). Those words are read aloud by a text-to-speech tool programmed to mimic T15's voice. From analyzing video-recorded conversational speech decoding sessions, we captured meta-data such as performance during noisy background events, time spent in casual and professional interactions, and different uses of the speech neuroprosthesis. We also discuss participant feedback and overall decoding accuracy. We found that the BCI performed consistently well across different types of noisy and calm environments. Over the first 9 months, T15 recorded over 250 hours of personally directed use, which was limited by the system requiring a researcher present to initiate it. Now the system can be initiated by a care partner, and T15's use hours have since been increasing rapidly. We also integrated the speech BCI's output into T15's standard consumer software. This started with implementing a Bluetooth keyboard that allowed T15 to type sentences on his computer for tasks such as sending a text message or browsing the web. We are now focusing on creating an application that can run on his personal computer to allow for more full-featured control over it. We demonstrate that the speech neuroprosthesis provided T15 with a means to communicate accurately, quickly, and naturalistically across a range of use cases. The implications of this work suggest that speech BCIs may be a viable alternative to current state of the art communication aids and are rapidly approaching a truly naturalistic option.

Disclosures: **H. Peracha:** None. **C. Iacobacci:** None. **N. Card:** None. **M. Wairagkar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent applications related to speech BCI owned by the Regents of the University of California. **X. Hou:** None. **T. Singer-Clark:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on patents related to BCI owned by Brown University. **L.R. Hochberg:** F. Consulting Fees (e.g., advisory boards); The MGH Translational Research Center has a clinical research support agreement with Neuralink, Synchron, Axoft, Precision Neuro, and Reach Neuro, for which LRH provides consultative input., Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC);, charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp., Patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); Advisor to wispr.ai and received equity. **D. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); Surgical consultant to Paradromics Inc.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.17/H28

Topic: E.05. Brain-Machine Interface

Support: NINDS Grant UH3NS114439

Title: Segmentation of spoken speech from unlabeled ECoG signals: A pilot study with an ALS participant

Authors: ***M. ANGRICK**[1], S. LUO[1], Q. RABBANI[1], S. JOSHI[1], D. CANDREA[1], G. W. MILSAP[2], C. GORDON[1], K. ROSENBLATT[1], L. CLAWSON[1], N. J. MARAGAKIS[1], F. TENORE[2], M. S. FIFER[2], N. F. RAMSEY[3], N. E. CRONE[1];
[1]The Johns Hopkins Univ., Baltimore, MD; [2]Johns Hopkins Applied Physics Lab., Laurel, MD; [3]UMC Utrecht Brain Ctr., Univ. of Utrecht, Utrecht, Netherlands

Abstract: Brain-Computer Interfaces (BCI) offer the opportunity to restore spoken communication in individuals with partial or complete loss of speech due to paralysis from amyotrophic lateral sclerosis (ALS), brainstem stroke, or other neurological disorders. Many prior efforts toward this goal have required time-aligned target representations for successful

model training - a major challenge when working with people who have already lost their voice, a scenario in which no ground truth is available. In this pilot study, we made a first step toward addressing this challenge. We employed a clustering approach for multivariate time series data to identify cognitive processes of speech production and used the resulting labels to train a voice activity detection (VAD) model based purely on neural signals. We evaluated our approach using held-out open-loop recordings of a single dysarthric clinical trial participant (ClinicalTrials.gov, NCT03567213) living with ALS, and we compared the resulting VAD performance against previous solutions trained with ground truth VAD information. Our approach achieved a median error rate of 0.5 seconds per trial with respect to actual spoken speech. While the results are not on par yet with models trained on ground truth VAD information, many instances of speech production can be segmented sufficiently, e.g., for BCI applications to prevent speech activity leaking into online baseline computations.

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Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.18/H29

Topic: E.05. Brain-Machine Interface

Support: A. P. Giannini Postdoctoral Fellowship
NIH-NIDCD (U01DC017844)
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DP2 from the NIH Office of the Director and managed by NIDCD (1DP2DC021055)
DOD CDMRP ALS Pilot Clinical Trial Award (AL220043)
Searle Scholars Program
Career Award at the Scientific Interface from the Burroughs Wellcome Fund

Title: Conversational speech decoding from the intracortical neural activity of a man with ALS

Authors: *N. S. CARD[1], C. IACOBACCI[1], H. PERACHA[1], M. WAIRAGKAR[1], X. HOU[1], T. SINGER-CLARK[1], L. R. HOCHBERG[2], D. M. BRANDMAN[3], S. D. STAVISKY[1];
[1]Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [2]Brown Univ., Providence, RI; [3]Neurolog. Surgery, Univ. of California, Davis, Sacramento, CA

Abstract: Communication is a priority for the millions of people living with dysarthria from brain injuries or neurological disorders such as stroke and amyotrophic lateral sclerosis (ALS). Brain-computer interfaces can enable rapid, intuitive communication for people with paralysis by transforming the cortical activity associated with attempted speech into text. Despite recent advances, speech brain-computer interfaces have been restricted by inaccurate word output. Here, we report a speech neuroprosthesis that was accurate enough to enable the user to have extensive conversations with family, friends, and colleagues for the first time in years.
A 45-year-old man ('T15') with ALS and severe dysarthria was enrolled into the BrainGate2 clinical trial. Four microelectrode arrays were placed in his left precentral gyrus to record neural activity from 256 intracortical electrodes. We trained a recurrent neural network to decode sequences of phonemes (i.e., the building blocks of words) from T15's neural signals as he attempted to speak. Phoneme sequences were assembled into the most likely words being spoken by a language model with a potential output vocabulary size of 125,000 words and displayed on a screen in real time. At the end of a sentence, the decoded words were played aloud using a text-to-speech tool that was programmed to sound like T15's pre-ALS voice. The recurrent neural network was continuously finetuned with new data to enable stable decoding over weeks of use. In a Copy Task where T15 attempted to say prompted sentences, we were able to decode his attempted speech with a word error rate of 2.5% at his self-paced speaking rate of 31.6 words per minute (WPM), which was over 4.5 times faster than his alternative means of communication: using a gyroscopic head mouse (6.3 ± 1.3 WPM; mean ± SD) or a skilled interpreter (6.8 ± 5.6 WPM). Next, we developed an unstructured Conversation Mode that enabled T15 to use the speech neuroprosthesis to speak to his family, friends, and colleagues. Over the course of more than 9 months, T15 used the speech neuroprosthesis in Conversation Mode in his own home for over 359 hours. The neuroprosthesis reliably detected his attempted speech with few false positives. Out of 32,432 sentences self-scored by the participant, 28,068 (86.5%) were decoded at least mostly correctly, and 17,959 (55.4%) were decoded completely correctly. Our speech neuroprosthesis reached a level of performance suitable to restore naturalistic communication, and T15 and his family preferred to use the speech neuroprosthesis over his alternative communication strategies.

Disclosures: **N.S. Card:** None. **C. Iacobacci:** None. **H. Peracha:** None. **M. Wairagkar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent applications related to speech BCI owned by the Regents of the University of California. **X. Hou:** None. **T. Singer-Clark:** None. **L.R. Hochberg:** F. Consulting Fees (e.g., advisory boards); The MGH Translational Research Center has a clinical research support agreement with Neuralink, Synchron, Axoft, Precision Neuro, and Reach Neuro, for which LRH provides consultative input.. Other; charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **D.M. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California.. F. Consulting Fees (e.g., advisory boards); Brandman is a surgical consultant to Paradromics Inc. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stavisky is an inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp., patent

applications related to speech BCI owned by the Regents of the University of California., Stavisky was an advisor to wispr.ai and received equity..

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.19/H30

Topic: E.05. Brain-Machine Interface

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Seed Grant from the ALS Association #23-SGP-652
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Searle Scholars Program
Career Award at the Scientific Interface from the Burroughs Wellcome Fund to Stavisky

Title: Brain-to-Voice: real-time voice synthesis from intracortical neural activity of a person with ALS

Authors: *M. WAIRAGKAR[1], N. S. CARD[1], C. IACOBACCI[1], T. SINGER-CLARK[1], X. HOU[1], L. R. HOCHBERG[2], D. M. BRANDMAN[1], S. D. STAVISKY[1];
[1]Dept. of Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [2]Neurology/Engineering, Massachusetts Gen. Hospital/ Brown University/ Harvard Med. School/ Providence VAMC, Boston, MA

Abstract: Losing the ability to speak due to neurological disease is devastating. Intracortical brain computer interfaces (BCIs) can restore communication in people living with paralysis Recently, there has been rapid progress in decoding neural correlates of attempted speech into text. However, text does not capture the full range of natural expressive prosodic speech, including changes in cadence, pace, intonations, and volume. As the next step in speech BCIs, we present a real-time brain-to-voice neuroprosthesis that continuously synthesizes voice from intracortical neural activity of a person with ALS with instantaneous audio feedback.
As part of the ongoing BrainGate2 clinical trial, ‘T15’, a 45-year-old man with severe dysarthria due to ALS was implanted with four Utah arrays (256 total electrodes) in his ventral and middle precentral gyrus. We recorded hundreds of individual neurons as T15 attempted to speak (vocalizing unintelligibly). The major challenge to synthesizing voice was the lack of ground truth for what T15 sounds like or is trying to say for training the BCI. To overcome this, we synthetically generated target training data speech from known text cues using text-to-speech and time-aligned it with T15’s neural activity. We built a Transformer model to decode neural activity into low-dimensional spectral and pitch features which were converted by a vocoder into audible speech. Speech samples were decoded within 10 ms allowing real-time synthesis.

As T15 attempted to speak, his neural activity was instantaneously transformed into nearly intelligible synthesized speech in real-time and played back to him in closed loop (Pearson correlation r=0.90±0.05 with target speech). The BCI was generalizable, which allowed T15 to produce a variety of vocalizations including spelling words out, interjections, pseudo-words and speaking by miming without vocalizing, without training on these tasks. T15 also used the voice neuroprosthesis for self-directed conversation. Additionally, we trained the BCI to synthesize speech in T15's own (pre-ALS) voice. We also decoded para-linguistic features such as pitch changes in T15's attempted speech allowing him to modulate intonations in synthesized speech in closed loop, making his BCI-voice more expressive.
Taken together, these results demonstrate a truly closed-loop continuous and causal naturalistic voice synthesis BCI. Our flexible approach is not dependent on a language model, discretized tokens, or fixed vocabulary. By mapping neural activity to a continuous speech output space, it generalizes to vocalize a variety of sounds that support naturalistic expressive communication.

Disclosures: M. Wairagkar: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application related to speech BCI owned by the Regents of the University of California. **N.S. Card:** None. **C. Iacobacci:** None. **T. Singer-Clark:** None. **X. Hou:** None. **L.R. Hochberg:** Other; Research agreements through MGH Translational Research Center: Neuralink, Synchron, Axoft, Precision Neuro, and Reach Neuro for which LRH provides consultative input., Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC), Charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **D.M. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); Surgical consultant at Paradromics. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent applications related to speech BCI owned by the Regents of the University of California, Licensed Stanford IP.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.20/H31

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N2864C, A4820R, A2295R, A3803R)
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CAUTION: Investigational Device. Limited by Federal Law to Investigational Use

Title: A large vocabulary intracortical speech neuroprosthesis for a locked-in person with anarthria

Authors: *J. JUDE[1,2], S. HARO[3], H. LEVI-AHARONI[4,2], A. ACOSTA[5], S. ALLCROFT[6], N. CARD[7], M. WAIRAGKAR[8], D. BRANDMAN[9], S. D. STAVISKY[8], J. D. SIMERAL[10,6,11], L. R. HOCHBERG[10,12,4,13,11], D. B. RUBIN[4,2];
[1]Massachusetts Gen. Hosp., Providence, RI; [2]Neurology, Harvard Medical School, Boston, MA; [3]Brown Univ., Providence, RI; [4]Ctr. for Neurotechnology and Neurorecovery, Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [5]Massachusetts Gen. Hosp., Boston, MA; [6]Sch. of Engin., Brown Univ., Providence, RI; [7]Bioengineering, Univ. of California, Davis, Davis, CA; [8]Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [9]Neurolog. Surgery, UC Davis Hlth., Sacramento, CA; [10]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Dept. of VAMC, Providence, RI; [11]Carney Inst. for Brain Sci., Brown Univ., Providence, RI; [12]School of Engineering, Brown University, Providence, RI; [13]Neurology, Harvard Med. Sch., Boston, MA

Abstract: Intracortical brain-computer interfaces (iBCIs) intended for decoding speech have recently been shown to provide individuals with ALS and severe dysarthria an intuitive method of high-throughput communication (Willett et al. 2023 Nature, Card et al. 2023 medRxiv). These advances have been demonstrated in individuals who, although dysarthric, are still able to vocalize and move speech articulators. In this work, we present a speech iBCI that decodes from 6 microelectrode arrays (each composed of 64 electrodes for a total of 384 recording channels) placed in the left precentral gyrus of a 33 year old Braingate clinical trial participant. This participant has anarthria, quadriplegia, and complete ventilatory-dependence due to advanced ALS; his primary mode of communication is through eye movements and he has not spoken in any capacity in over 2 years. Our iBCI decodes the intended movements of the muscles of articulation during attempted speech and uses a recurrent neural network (RNN) based phoneme decoder, combined with a language model, to decode attempted speech based on neural activity in speech related areas of the motor cortex. Although this has previously been shown to be an effective decoding strategy, there are additional challenges involved with decoding attempted speech from a participant with complete anarthria and ventilator-dependence pertaining to timing, the loss of control over spontaneous respiration, and the lack of real-time auditory and somatosensory feedback. When initially tested on a standard 50-word vocabulary, our speech neuroprosthesis achieves a 77.8% word accuracy rate. We then extend this to a conversational 125,000-word vocabulary, where it achieves a phoneme accuracy rate of 71% and a subsequent

word accuracy rate of 66% when training the decoder on a total of 1400 sentences, with a speaking rate of 30 words per minute. These results show that attempted speech decoding is feasible from people with anarthria and ventilator-dependence, thus demonstrating the ability to restore a high level of communication to those even with complete speech motor paralysis.

Disclosures: J. Jude: A. Employment/Salary (full or part-time):; Massachusetts General Hospital. **S. Haro:** A. Employment/Salary (full or part-time):; Brown University. **H. Levi-Aharoni:** None. **A. Acosta:** A. Employment/Salary (full or part-time):; Massachusetts General Hospital. **S. Allcroft:** A. Employment/Salary (full or part-time):; Brown University. **N. Card:** A. Employment/Salary (full or part-time):; University of California, Davis. **M. Wairagkar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. **D. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); surgical consultant to Paradromics Inc. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California, inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp.. F. Consulting Fees (e.g., advisory boards); advisor to wispr.ai and received equity.. **J.D. Simeral:** None. **L.R. Hochberg:** F. Consulting Fees (e.g., advisory boards); The MGH Translational Research Center has a clinical research support agreement (CRSA) with Axoft, Neuralink, Neurobionics, Precision Neuro, Synchron, and Reach Neuro, co-investigator on an NIH SBIR grant with Paradromics, and is a non-compensated member of the Board of Directors of a nonprofit assistive communication device technology foundation (Speak Your Mind), Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC);, charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC. **D.B. Rubin:** None.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.21/H32

Topic: E.05. Brain-Machine Interface

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NeuralStorm NRT Award #2152260 to Singer-Clark
DP2 from the NIH Office of the Director and managed by NIDCD (1DP2DC021055) to Stavisky
Searle Scholars Program to Stavisky
Career Award at the Scientific Interface from the Burroughs Wellcome

Fund to Stavisky
CAUTION: Investigational Device. Limited by Federal Law to Investigational Use. The contents do not represent the views of the National Institutes of Health or the Department of Veterans Affairs or the United States Government.

Title: Brain-computer interface cursor control driven by speech motor cortex

Authors: *T. SINGER-CLARK[1], C. IACOBACCI[2], N. CARD[3], M. WAIRAGKAR[4], X. HOU[5], F. KAMDAR[6], D. AVANSINO[7], J. M. HENDERSON[8], L. HOCHBERG[9,10], S. D. STAVISKY[4], D. BRANDMAN[11];
[1]Univ. of California, Davis, Davis, CA; [2]Univ. of California, Davis, Pacifica, CA; [3]Bioengineering, Univ. of California, Davis, Davis, CA; [4]Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [5]UC Davis, Davis, CA; [6]Stanford Univ., Moutnain View, CA; [7]Electrical Engin., Neurosurg., Stanford Univ., San Mateo, CA; [8]Dept Neurosurgy, R 227, Stanford Univ., Stanford, CA; [9]Massachusetts Gen. Hosp., Boston, MA; [10]Brown University, Providence, RI; [11]Neurolog. Surgery, UC Davis Hlth., Sacramento, CA

Abstract: Intracortical brain-computer interfaces (iBCIs) can restore communication capabilities for people with paralysis due to neurological disease or injury such as ALS or stroke. Typically, iBCIs for controlling a computer are driven by neural activity recorded from electrodes in the predominantly hand-related dorsal precentral gyrus (dPCG). In contrast, iBCIs for speech are driven by the predominantly speech- and orofacial-related ventral precentral gyrus (vPCG). Because the cortical coverage of an iBCI is currently limited by constraints on the number of electrodes that can be implanted and on the craniotomy size, a decision must be made as to which brain area(s) to target. It was previously unknown whether an iBCI could enable both cursor and speech functionality if all the electrodes were implanted in vPCG (to maximize speech decoding accuracy). In this study, we demonstrate cursor control driven by neural activity recorded from intracortical microelectrodes in vPCG. A cursor iBCI was used by two BrainGate2 clinical trial participants ("T15" and "T12") with ALS. T15 had four 64-electrode Utah arrays in vPCG and T12 had two such arrays in vPCG. Both participants had previously operated a speech iBCI [Card et al. 2023, medRxiv, Willett et al. 2023]. In T15's very first usage of a cursor iBCI, he successfully gained closed-loop control of the cursor within 41 seconds of beginning calibration. In a grid target selection task, participants achieved bitrates as high as 1.8 (T15) and 1.2 (T12) bits per second (average 1.7 bps and 1.1 bps). Additionally, participants were able to control the cursor using multiple different types of imagery, including attempted hand, head, and tongue movement imageries. We observed that cursor control using attempted hand movement imagery was perturbed by simultaneous speech, but offline analyses suggest this can be mitigated by including a small amount of simultaneous attempted cursor movement and speaking data in the decoder's training data. Taken together, these results suggest that iBCI users may be able to have arrays placed in vPCG (speech motor cortex) in order to operate both a cursor iBCI and a speech iBCI, instead of having to split arrays between ventral and dorsal motor areas. This offers communication neuroprostheses additional flexibility to provide multimodal BCI functionality while still having sufficiently high channel counts in ventral motor areas to support accurate speech decoding.

Disclosures: T. Singer-Clark: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventor on

patents related to BCI owned by Brown University. **C. Iacobacci:** None. **N. Card:** None. **M. Wairagkar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. **X. Hou:** None. **F. Kamdar:** None. **D. Avansino:** None. **J.M. Henderson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp., shareholder in Maplight Therapeutics. F. Consulting Fees (e.g., advisory boards); consultant for Neuralink Corp, serves on the Medical Advisory Board of Enspire DBS. **L. Hochberg:** F. Consulting Fees (e.g., advisory boards); he MGH Translational Research Center has a clinical research support agreement with Neuralink, Synchron, Axoft, Precision Neuro, and Reach Neuro, for which LRH provides consultative input. Other; Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC), charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp, patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); was an advisor to wispr.ai and received equity. **D. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); surgical consultant to Paradromics Inc.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.22/H33

Topic: E.05. Brain-Machine Interface

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NIH NIDCD (U01DC017844, R01DC014034, U01DC019430, K23DC021297,1DP2DC021055)
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A.P. Giannini Postdoctoral Fellowship to N. Card
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, or the Department of Veterans Affairs or the United States Government.

CAUTION: Investigational Device. Limited by Federal Law to Investigational Use.

Title: An intuitive, bimanual, thirty-way, high-throughput sequence to sequence QWERTY keyboard typing neuroprosthesis

Authors: J. JUDE[1,2], S. ALLCROFT[3], A. ACOSTA[1], N. CARD[4], M. WAIRAGKAR[4], S. D. STAVISKY[4], D. BRANDMAN[4], J. D. SIMERAL[5,6], L. HOCHBERG[1,2,7,6,8], *D. RUBIN[1,2]; [1]Neurol., Massachusetts Gen. Hosp., Boston, MA; [2]Neurology, Harvard Medical School, Boston, MA; [3]Sch. of Engin., Brown Univ., Providence, RI; [4]Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [5]DVA, Ctr. for Neurorestoration and Neurotechnology (CfNN), Providence, RI; [6]School of Engineering, Brown University, Providence, RI; [7]Department of Veterans Affairs, Center for Neurorestoration and Neurotechnology (CfNN), Providence, RI; [8]Robert J. and Nancy D. Carney Institute for Brain Science Institute for Brain Science, Brown University, Providence, RI

Abstract: Keyboard typing represents a high information rate communication paradigm that most people are familiar with. In this work we introduce an intracortical brain computer interface (iBCI) typing neuroprosthesis that mimics a bimanually controlled QWERTY keyboard layout and corresponding typing imagery. Our neuroprosthesis represents an intuitive, familiar, and easy-to-learn communication device for individuals with quadriplegia caused by ALS and related conditions.

The keyboard is comprised of 3 adjacent rows of keys, with 10 keys on each row. By decoding three discrete attempted/intended movements on each of the ten digits of the bilateral hands, the user is able to select any of the 30 keys at any time. The upper row is accessed by attempting to extend each of the user's 10 fingers forward from a resting position. The middle row is accessed by attempting finger flexion straight downwards, perpendicular to the plane of the palm. The bottom row is accessed by the user attempting to curl each finger into the palm of the hand. After each attempted finger movement, the user is instructed to return to a neutral resting position before attempting to type the next key. Typing is completely self-paced, therefore the speed of communication is potentially far greater than alternative augmentative communication devices that rely on fixed decoding intervals.

We tested our QWERTY keyboard alongside a recurrent neural network (RNN) decoder paired with a language model which finalizes the decoded sentence from the RNN output lattice. We decoded from 6 microelectrode arrays (384 total microelectrodes) placed in the left precentral gyrus of a Braingate clinical trial participant typing sentences constructed from a standardized 50-word vocabulary. This participant has quadriplegia , anarthria, and complete ventilatory-dependence due to advanced ALS; his primary mode of communication is through eye movements. Using this interface, we attained a character error rate of 19% with an average of 28 characters typed per minute. With the language model applied to the outputs of the RNN the system achieved a character error rate of 9.2% and a resulting word error rate of 9.1%.

When paired with a language model, the use of the QWERTY keyboard layout has the added advantage of reducing decoder confusion, as the keys assigned to each finger (i.e., the three keys in a given column of the QWERTY keyboard) are unlikely to be contiguous with each other when correlated with the statistics of the English language. We believe that this communication paradigm may have the potential to provide a rapid, highly-accurate, and intuitive means of communication for people with communication deficits due to paralysis.

Disclosures: **J. Jude:** None. **S. Allcroft:** None. **A. Acosta:** None. **N. Card:** None. **M. Wairagkar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MW has patent applications related to speech BCI owned by the Regents of the University of California. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); S. Stavisky is an inventor on intellectual property owned by Stanford University that has been licensed to Blackrock Neurotech and Neuralink Corp., S. Stavisky has patent applications related to speech BCI owned by the Regents of the University of California., S. Stavisky was an advisor to wispr.ai and received equity. **D. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); D. Brandman has patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); D. Brandman is a surgical consultant to Paradromics Inc.. **J.D. Simeral:** None. **L. Hochberg:** F. Consulting Fees (e.g., advisory boards); The MGH Translational Research Center has a clinical research support agreement (CRSA) with Axoft, Neuralink, Neurobionics, Precision Neuro, Synchron, and Reach Neuro; LRH provides consultative input. Other; LRH is a co-investigator on an NIH SBIR grant with Paradromics, LRH is a non-compensated member of the Board of Directors of a nonprofit assistive communication device technology foundation (Speak Your Mind Foundation), Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC);, charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort.. **D. Rubin:** None.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

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Topic: E.05. Brain-Machine Interface

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NIH NINDS (U01NS123101)
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CAUTION: Investigational Device. Limited by Federal Law to Investigational Use

Title: Assistive Virtual Typing Using Mixed Gesture Decoding in a Single-Hemisphere Intracortical Brain-Computer Interface

Authors: *N. C. HERRICK[1,2], S. E. LÜTSCHG ESPINOSA[1], T. HOSMAN[1,3,2], C. NICOLAS[4], A. ACOSTA[4], S. ALLCROFT[1,2], C. E. VARGAS-IRWIN[5,3,2], L. R. HOCHBERG[6,1,4,7,3], J. D. SIMERAL[6,1,3];
[1]Sch. of Engin., Brown Univ., Providence, RI; [2]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Dept. of VA Med. Ctr., Providence, RI; [3]Carney Inst. for Brain Sci., Brown Univ., Providence, RI; [4]Ctr. for Neurotechnology and Neurorecovery, Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [5]Dept. of Neurosci., Brown Univ., Providence, RI; [6]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Dept. of VAMC, Providence, RI; [7]Dept. of Neurol., Harvard Med. Sch., Boston, MA

Abstract: Intracortical brain-computer interfaces (iBCIs) are being developed to enable communication for individuals with paralysis by decoding their intended actions from neural signals, allowing them to control assistive devices. While some individuals may benefit from speech-to-text applications, these are unsuitable for people with difficulty speaking, such as those with advanced ALS. In this study, we extend our previous demonstration of iBCI-enabled 10-digit typing (Prog. No. 488.01, SfN 2023) to now include decoded hand gestures for switching between rows of a virtual keyboard and continuous, uncued neural decoding to enable a free-paced typing paradigm. We recorded neural activity from the precentral gyrus of two participants with tetraplegia enrolled in the BrainGate2 pilot clinical trial to enable typing on an iBCI-controlled keyboard using attempted hand gestures. The onscreen virtual keyboard provided four rows of ten keys each, in a QWERTY layout, including letters, numbers, and a few special characters. Attempted finger or thumb movements were decoded to select one of 10 keys in the active keyboard row. A new feature of the neural decoder enabled participants to change the active keyboard row up (or down) at any time by imagining wrist extension (or flexion). Participants completed several tasks to quantify typing performance using the 13-class LDA-HMM decoder (10 digits, 2 wrist movements, and a no-action state). A cued sentence-copy task required participants to navigate through the keyboard rows and select individual keys using wrist and digit imagery sequences. This cued task included a 2-second cue period, followed by a 1-second inter-trial interval; the cued structure inherently limited the application's maximum correct characters per minute (CCPM) and bit rate. The typing speed was improved in a more practical task in which participants navigated the keyboard to copy a sentence at their own pace, without predetermined inter-character or row-switch intervals. Allowing the participant to proceed at their own typing pace improved the bit rate from an average of .56 bits per second in the fixed-paced study to 1.7 bits per second (mean 13 CCPM) while maintaining a typing accuracy of 82.75%. By creating a typing tool that is both intuitive and efficient, we aim to enable individuals with severe disability to engage in text-based communication effortlessly.

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and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **J.D. Simeral:** None.

Poster

PSTR030: Advances in Speech Prostheses

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.24/H35

Topic: E.05. Brain-Machine Interface

Support: Emory Neuromodulation and Technology Innovation Center (ENTICe)
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Title: Population dynamics of cursor control with brain-computer interfaces

Authors: *Y. H. ALI[1,2], D. MIFSUD[2,1], M. RIGOTTI-THOMPSON[1,2], S. R. NASON-TOMASZEWSKI[1], A. PRITCHARD[1,2], P. BECHEFSKY[1], N. AU YONG[1], L. R. HOCHBERG[3,4,5,6,7], C. PANDARINATH[1,2];
[1]Emory Univ., Atlanta, GA; [2]Georgia Inst. of Technol., Atlanta, GA; [3]Ctr. for Neurotechnology and Neurorecovery, Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [4]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Rehabil. R&D Service, Providence VA Med. Ctr., Providence, RI; [5]Carney Inst. for Brain Sci., [6]Sch. of Engin., Brown Univ., Providence, RI; [7]Dept. of Neurol., Harvard Med. Sch., Boston, MA

Abstract: Intracortical brain-computer interfaces (iBCIs) have enabled people with tetraplegia to control assistive devices, like computers, by decoding movement intent from neural recordings. While iBCI decoders often assume a direct representation of movement kinematics in neural activity, neural populations also have internal dynamics that do not directly encode kinematic variables but are still involved in the task. We hypothesized that, during iBCI control, these internal dynamics would be present in the neural activity even when the neural population is confined to using a linear decoder for cursor control. Neural activity was recorded from participant T16, a 52-year-old female with chronic tetraplegia and dysarthria due to a pontine stroke. T16 had four 64-channel intracortical microelectrode arrays (Blackrock Neurotech)

placed in her precentral gyrus, including two in the hand knob (area 6d). Using a linear decoder, T16 performed cursor control on a 6-by-6 grid task, in which she moved the cursor to each cued target and held it there for 1.5 seconds to select it. Binned spike counts were modeled with Latent Factor Analysis via Dynamical Systems (LFADS) offline to yield denoised single-trial estimates of neural population activity. Using these firing rate estimates, we explored whether the population activity was acting as a direct encoding of the cursor velocity. If it was, then one would expect that we could perform the reverse transformation to predict the neural data from the velocity with high accuracy. Instead, we found that, while kinematics could be accurately predicted from neural activity with a linear decoder (R^2 of 0.42), neural activity could not be predicted well from kinematics (R^2 of 0.061). However, if the training data was split up according to how far into the trial each sample was measured ("trial time") and a different linear decoder was used for each of these groups, then the kinematics-to-neural prediction improved (R^2 of 0.16). This suggests that the neural population has time-varying activity that is independent of kinematics and is not well-explained by a static encoding of kinematics in neural activity. We also measured "tangling", which quantifies the degree to which a time-varying signal exhibits different derivatives for the same state. Using this metric, we found that, at the onset of the target cue, the neural population began in a high-tangling state (0.85 mean ± 0.72 std) and then dropped to a low-tangling state (0.070 mean ± 0.032 std) at movement initiation. These findings, consistent with prior results in non-human primates, suggest that the neural population acts like a dynamical system during closed-loop iBCI control.

Disclosures: Y.H. Ali: None. **D. Mifsud:** None. **M. Rigotti-Thompson:** None. **S.R. Nason-Tomaszewski:** None. **A. Pritchard:** None. **P. Bechefsky:** None. **N. Au Yong:** None. **L.R. Hochberg:** Other; MGH Translational Research Center has a clinical research support agreement with Axoft, Neuralink, Neurobionics, Precision Neuro, Synchron, and Reach Neuro, for which LRH provides consultative input., LRH is a co-investigator on an NIH SBIR grant with Paradromics., LRH is a non-compensated member of the Board of Directors of a nonprofit assistive communication device technology foundation (Speak Your Mind Foundation)., Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC)., Charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **C. Pandarinath:** F. Consulting Fees (e.g., advisory boards); Synchron, Meta (Reality Labs).

Poster

PSTR031: Higher Order Control, Multi-Task Integration, and Theory of Posture and Gait

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.01/H36

Topic: E.06. Posture and Gait

Support: Natural Sciences and Engineering Research Council of Canada Discovery Grant (RGPIN-2021-03637

Title: Prefrontal cortex activity during complex gait dual-tasking in young- and middle-aged adults

Authors: *L. KRELOVE[1], A. MACHULA[2], L. E. SERGIO[2], G. MOCHIZUKI[2];
[1]Fac. of Sci., [2]Sch. of Kinesiology and Hlth. Sci., York Univ., Toronto, ON, Canada

Abstract: Daily life involves allocating attention between simultaneous tasks, such as walking while talking. However, this "dual-tasking" (DT) is known to be distracting and increases demand on attentional control networks. The prefrontal cortex (PFC) directs executive function, which includes the division of attention between motor and cognitive tasks. Due to age-related brain changes, older adults rely more on the PFC than young adults (YA), such that they process balance-distractor conflicts differently and prioritize balance control. The result is that less attention is paid by the individual towards the environment. It is not known at what point during the transition to older adulthood that brain changes begin to impact behaviour, balance, and fall risk. This work aims to characterize changes in PFC activity linked with age-related attentional shifts in relation to balance control in middle-aged adults, and to probe if a cortical marker of postural stability during distraction may be present. The present study investigated PFC activity using functional near-infrared spectroscopy (fNIRS) during complex gait DT in an augmented reality (AR) enhanced environment with and without cognitive distraction. Gait and attention capacity were challenged in YA (n=20, mean age 23.9 ± 4.7 years, 10 female) and middle-aged adults (MA; n=10, mean age 57 ± 4.9 years, 5 female). Participants walked at a comfortable pace on a pressure-sensitive gait mat to collect spatiotemporal metrics without distraction or obstacles, while avoiding virtual AR obstacles, experiencing a working memory recall distractor, and the combined challenge of obstacle avoidance during distraction. Throughout, fNIRS measured PFC activity as an attention indicator. It was hypothesized that PFC activity would be higher in MA than YA across conditions and increase with task complexity, and that MA would not modulate gait to the same extent as YA. We observed lower PFC activity in MA versus YA across conditions. We also observed decreased gait velocity and increased step variability in both groups with the introduction of obstacles and distraction, which are indicators of cautious gait patterns. There is an emerging significant relationship between PFC activity and gait velocity (Spearman's rho = -0.386) and cadence (Spearman's rho = -0.475) appearing during obstacle avoidance while distracted. These findings show that MA have altered PFC activation compared to YA during complex gait DT, and seek more stability during complex DT walking. These data suggest that neural changes in attention and balance control have begun in middle aged adults transitioning to older adulthood and are linked to behaviour.

Disclosures: L. Krelove: None. **A. Machula:** None. **L.E. Sergio:** None. **G. Mochizuki:** None.

Poster

PSTR031: Higher Order Control, Multi-Task Integration, and Theory of Posture and Gait

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.02/H37

Topic: E.06. Posture and Gait

Support: Natural Sciences and Engineering Research Council of Canada Discovery Grant (RGPIN-2021-03637)

Title: The effect of distraction and sway feedback on prefrontal cortex activation and balance in young and middle-aged adults

Authors: L. KRELOVE[1], *G. MOCHIZUKI[2];
[1]Fac. of Sci., [2]Sch. of Kinesiology and Hlth. Sci., York Univ., Toronto, ON, Canada

Abstract: Humans are generally able to maintain balance when performing simultaneous tasks without falling. This "dual-tasking" (DT) is common in daily life but divides attention, increasing demand on attentional networks. The prefrontal cortex (PFC) directs executive function, including allocating attention between motor tasks and secondary activities. With age, more active attention is needed to remain upright and may reduce awareness of environmental challenges, which can increase fall risk. Unlike young adults (YA) who allocate attention to cognitive tasks, older adults tend to prioritize stability limitations in attentional resources to complete secondary tasks. It is unknown if the focus of attention (internal vs external) for balance influences the effects of distraction on the control of stability. Knowledge of these DT effects in adults transitioning to older adulthood is also limited. The present study probes the effect of distraction and focus of attention for balance information on PFC activity in YA and middle aged (MA) adults. This work investigated if MA (age 46-65; n=15, mean age 57.2 ± 4.8 years, 4 female) show cortical activity similar to YA (n=20, mean age 24.9 ± 4.7 years, 9 female), or if there is evidence of differences between ages associated with neural correlates of attention. Functional near-infrared spectroscopy (fNIRS) measured blood oxygen level in the PFC during quiet standing cognitive-motor DT. Participants stood on a forceplate collecting centre-of-pressure (COP) data to measure postural control. The cognitive DT challenge involved backward serial-seven counting and visual feedback. Participants either fixed their gaze on an external target or viewed their real-time postural sway from the forceplate on a screen to create 4 experimental conditions: single-task fixed; single-task sway; DT fixed; DT sway. It was hypothesized that MA internally direct attention more often than YA, as illustrated by increased PFC activity in the DT-sway condition. Preliminary analysis indicated that MA show elevated PFC activation during DT-sway (when attention was directed internally). In addition, the area of the COP 95% confidence ellipse was higher for MA, especially for the DT-sway condition. MA show cognitive and behavioural changes which are different from YA, suggesting reduced DT capacity and an inability to direct attention externally based on task demands. This reinforces the high cognitive demand and behavioural cost of DT and indicates that DT capacity begins to decline in the transition to older adulthood.

Disclosures: L. Krelove: None. **G. Mochizuki:** None.

Poster

PSTR031: Higher Order Control, Multi-Task Integration, and Theory of Posture and Gait

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.03/H38

Topic: E.06. Posture and Gait

Support: Italian Multiple Sclerosis Foundation (FISM) Grant 2022/R-Multi/021

Title: Effects of speed and the use of handrails on cortical activity patterns during treadmill walking

Authors: *L. BONZANO[1], M. BIGGIO[1], C. IESTER[1], D. CATTANEO[2], S. CUTINI[3], A. BISIO[1], L. PEDULLÀ[4], A. TORCHIO[2], M. BOVE[1];
[1]Univ. of Genoa, Genoa, Italy; [2]IRCCS Fondazione Don Carlo Gnocchi ONLUS, Milan, Italy; [3]Univ. of Padova, Padua, Italy; [4]Italian Multiple Sclerosis Fndn., Genoa, Italy

Abstract: In the rehabilitation field the use of treadmill handrails is debated, but it has been studied from a behavioral view. Indeed, it induces bad posture and prevents the natural stride. In order to give new hints in this frame, we explored the cortical correlates of treadmill walking at different speeds, holding or not onto the handrails. With fNIRS we assessed cortical activity in 24 healthy participants (27.0±6.3 y, 13 F). A box-car paradigm was designed, with 30 s of walking on a treadmill and 30 s of rest in an upright position. Participants walked in 4 randomized conditions (8 times each): the speed was set at 3 km/h or 5 km/h, and they kept their hands on the handrails (V3_HOLD and V5_HOLD conditions, respectively) or walked with a spontaneous swing of the arms (V3_no-HOLD and V5_no-HOLD conditions, respectively). During the rest blocks, they kept their hands on the handrails or their arms along the body, according to the related task condition. Sixteen sources and 16 detectors formed 44 standard channels (3 cm) covering frontal, prefrontal, sensorimotor and parietal areas. In addition, 8 short-separation (SS) channels (8 mm) were used. The fNIRS signal was pre-processed through custom scripts based on Homer3 (spline and wavelet motion correction techniques; band-pass filter (0.01-3 Hz)). A General Linear Model was applied, regressing the most correlated SS channel signal to reduce the physiological noise. HbO concentration changes of channels belonging to the same hemisphere and Brodmann's Area (BA) were averaged. Additionally, we assessed task-based BA-to-BA functional connectivity (FC). HbO concentration changes were influenced by task condition (Friedman's ANOVA with Bonferroni correction). Specifically, cortical activation elicited by the task in the no-HOLD condition was significantly higher at 5 km/h than 3 km/h in the left BA10, BA3 and BA39, and right BA10, BA9, BA8, BA3, and BA40. HbO concentration changes in the left BA40 were significantly higher at 5 km/h than 3 km/h, both in the no-HOLD and in the HOLD condition. The analysis of task-based BA-to-BA pairwise FC showed that the correlation value between L-BA10 and L-BA40 was statistically different: it was close to zero in the V3_HOLD condition, but it was very high (r=0.80) in the V5_no-HOLD condition. Speed (3 or 5 km/h) affects cortical activation during treadmill walking, and differences in activation between speeds are reduced when using the handrails. Also, stronger functional connectivity occurs at the higher speed and no handrails use. We suggest that speed and the use of handrails play a role in walking cortical activity patterns, thus they are key ingredients when planning a rehabilitation program.

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Poster

PSTR031: Higher Order Control, Multi-Task Integration, and Theory of Posture and Gait

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.04/H39

Topic: E.06. Posture and Gait

Title: Gait characteristics in college athletes during dual-task conditions

Authors: *C. CHAU, M. HURLEY, K. KEUHN, S. LEMAIRE, C. MARTIN, A. MONACO, T. COUGHLIN, K. DOWDALL, M. GELDER;
Nazareth Univ., Rochester, NY

Abstract: This study investigates the gait characteristics of college athletes and non-athletes while performing a concurrent cognitive task. Seventeen young adults ages 18-25 years old (nine non-athletes and eight athletes) were recruited from Rochester, NY. Participants performed two cognitive tests, serial subtraction (S) and an auditory Stroop test (A). Walking was recorded by the Vicon 3D motion capture system (Nexus) using eight cameras. Twenty-two 14 mm retro-reflective markers were placed on the skin of predetermined anatomical landmarks of the lower extremities, and seven body segments were reconstructed (CGM 1.1). Anatomical joint angles were calculated. Each participant completed 4 trials of walking (20 ft) without a concurrent task (Single-Task (ST)) or with a concurrent cognitive task (Dual-Task (DT)), either DTS or DTA, in a randomized order. The only constraint for all walking tasks is that the participant may not stop during walking trials. Spatiotemporal and kinematic gait parameters were processed by Visual3D software (C-Motion). Joint angular excursion for the pelvis, hip, knee, and ankle joints was calculated. Angle-angle diagrams were plotted to examine intralimb coordination. A one-way repeated measures ANOVA was used to compare the gait difference between the three walking conditions. A two-factor repeated measures ANOVA was used to compare the results between athletes and non-athletes. Results from athletes showed a significant decrease in stride length and hip joint excursion during DT-walking for both DTS (-0.1 m, -2º) and DTA (-0.11m, -2.7º) tasks as compared to ST-walking, respectively. A significant decrease in speed (-0.13m/s) and ankle joint excursion (-2.1º) was found during DTS walking as compared to ST walking. The changes in spatiotemporal parameters in athletes during DT-walking were similar to the non-athletes but to a lesser extent. The dual-task cost for speed was 9.5 for athletes and 11.6 for non-athletes during DTS walking. The ankle joint excursion was increased in athletes during ST (+3.2º) and DTS (+2.4º) tasks, with a concomitant slight decrease in the hip joint excursion (-1.5º, -1.5 º) compared to non-athletes, respectively. A significant decrease in cognitive error was found between athletes (3.09 ± 3.33%) and non-athletes (16.56 ± 3.32%) during DTS walking. Our results suggest that athletes and non-athletes behave similarly in single- and dual-task situations; athletes can tolerate a higher cognitive demand with fewer kinematic and spatiotemporal deviations compared to non-athletes. Athletes may also differ from non-athletes in strategies used to maintain balance during locomotion.

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Poster

PSTR031: Higher Order Control, Multi-Task Integration, and Theory of Posture and Gait

Location: MCP Hall A

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Program #/Poster #: PSTR031.05/H40

Topic: E.06. Posture and Gait

Support: NIH National Institute On Aging R01AG072756
NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development F32HD105458

Title: Test-retest reliability of perturbation-evoked cortical activity reflects stable individual differences in reactive balance control

Authors: *J. L. MIRDAMADI[1], A. M. PAYNE[2], A. POORMAN[1], K. JONES[1], G. MUNTER[1], L. H. TING[3], M. R. BORICH[1];
[1]Emory Univ., Atlanta, GA; [2]Florida State Univ., Tallahassee, FL; [3]Emory Univ. and Georgia Tech., Atlanta, GA

Abstract: There is a growing interest in measuring cortical activity during balance control for understanding mechanisms of impaired balance with aging and neurological dysfunction. The most well-characterized electrophysiological signal is the perturbation-evoked N1 potential that peaks 100-200 msec after a balance disturbance. We previously found associations between the N1 and individual differences in balance ability in younger and older adults, suggesting it may be a valuable electrophysiological biomarker of balance health. However, the clinical utility of the N1 response as a prognostic or monitoring tool will be limited by the reliability of its measurement, which has yet to be established. Here, we characterized reliability of the N1 response both within and between sessions in younger and older adults. 10 younger adults (YA) (24.3 ± 2.2 years) and 9 older adults (OA) (70.3 ± 5 years) completed two testing sessions of standing balance perturbations within one week. For all sessions, 64-channel electroencephalography (EEG) was recording while participants discriminated the direction of whole-body motion elicited by pairs of standing balance perturbations. We extracted N1 amplitude and latency from the Cz electrode, defined as the first and largest negative potential 100-300 msec post-perturbation. Internal consistency was quantified by comparing even and odd-numbered trials using the Spearman correlation coefficient (with the Spearman-Brown correction factor). Test-retest reliability was assessed using the intra-class correlation coefficient. The N1 amplitude and latency showed excellent internal reliability for each session and group ($r > 0.9$). When comparing internal reliability depending upon the number of trials analyzed, reliability plateaued within 6-10 trials for each session and group, indicating that a reliable measurement can be achieved in relatively few trials. N1 characteristics varied across individuals (amplitude: 8 µV - 70 µV, latency: 130 ms - 280 ms), yet within individuals, showed good or excellent test-retest reliability in YA (amplitude: $r = 0.88$, latency: $r = 0.95$) and excellent reliability in OA (amplitude: $r = 0.996$; latency: $r = 0.96$). Findings suggest that the N1 is stable within and across testing sessions and reflects individual-specific differences in balance control.

Our findings support the potential of the N1 as a reliable and stable electrophysiological biomarker suitable for longitudinal investigations, such as predicting falls and tracking treatment response.

Disclosures: J.L. Mirdamadi: None. **A.M. Payne:** None. **A. Poorman:** None. **K. Jones:** None. **G. Munter:** None. **L.H. Ting:** None. **M.R. Borich:** None.

Poster

PSTR031: Higher Order Control, Multi-Task Integration, and Theory of Posture and Gait

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.06/I1

Topic: E.06. Posture and Gait

Support: R01AG073152

Title: Neural Correlates of Reactive Balance Control Among Older Adults: The Possible Cortical Predominance

Authors: *R. PUROHIT[1], J. PITTS[2], L. KANNAN[3], T. S. BHATT[2];
[1]Univ. of Illinois at Chicago, Chicago, IL; [2]Physical Therapy, Univ. of Illinois at Chicago, Chicago, IL; [3]Physical Therapy, Northeastern Univ., Boston, MA

Abstract: Background: Neuroimaging studies commonly use mobile techniques (e.g., electroencephalography) to examine cortical correlates of reactive balance control (i.e., the ability to recover from unexpected disturbances like slips). However, mobile imaging techniques have poor spatial resolution, thus limiting access to subcortical structures and functional networks. In this study, we used functional MRI to examine imagined task-related cortico-subcortical activations and connectivity and their associations with reactive balance performance among older adults. **Methods**: Twenty older adults (72±7 years) underwent a single session of functional MRI with 3 conditions: imagined walking (IW), imagined slipping (IS) and rest. For task-related activations, we used SPM to build first level models and the subtraction method to create contrast images. Planned t-tests were performed between the three conditions (p=0.05, k=80) and xjview10 was used to extract the anatomical areas. Further, we used CONN software to determine resting-state FC between pre-selected atlases and networks associated with reactive balance, then performed correlations between FC and reactive stability. Participants also experienced a treadmill slip during standing. We quantified post-slipping center-of-mass state (reactive) stability using 3D motion analysis from the marker data affixed to the bony landmarks. **Results:** Neural activations were generally greater during both IW and IS than rest. IW showed greater activations in subcortical areas (e.g., cerebellum, basal ganglia, sub-lobar region) than rest; but IS had greater activations in cortical and subcortical areas (e.g., frontal lobes, primary motor cortices, cerebellum, and insula) than rest. IS also showed greater activations in cortical areas (e.g., pre-frontal lobes, primary motor cortices, supplementary motor area) than IW. Reactive stability significantly correlated with resting state FC within different cerebellar regions

(R^2<0.15, p<0.05), between the cerebellum-sensorimotor network *(R^2=0.12, p<0.05),* and between the cerebellum-dorsal attention network *(R^2=0.12, p<0.05).* **Discussion and conclusion:** The study findings suggest higher cortical involvement in reactive balance compared to unperturbed gait control among older adults. Compared to IW, increased activation during IS could be associated with greater recruitment of resources for sensorimotor processing of perturbation as well as higher cognitive and perceptual demands to recover from perceived balance loss. Lastly, FC within cortico-subcortical areas at rest could be associated with age-related alterations in reactive balance control.

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Poster

PSTR031: Higher Order Control, Multi-Task Integration, and Theory of Posture and Gait

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.07/I2

Topic: E.06. Posture and Gait

Support: Marsh Fund University of Wisconsin Foundation

Title: Standing balance disruption by virtual reality headset

Authors: *K. GRUBEN[1], J. FOX[2], J. BARTLOFF[3];
[1]Univ. Wisconsin, Madison, WI; [2]Mechanical Engin., Univ. of Wisconsin, Madison, Madison, WI; [3]Univ. of Wisconsin-Madison, Madison, WI

Abstract: The control of upright posture during human quiet standing typically incorporates visual feedback. Virtual Reality Headsets (VRH) display a three-dimensional representation that does not fully replicate the physical environment due to limitations in image resolution, field-of-view, and update rate. In addition, the headsets exert forces on the head due to weight and inertia. These factors alter visual and proprioceptive inputs that may change the control of upright posture.
The aim of this study was to isolate some of these factors to assess their effect on the neural control of quiet standing. Coordination of multiple muscles interacts with complex body dynamics to produce the force of the feet on the support surface (F). Within narrow frequency bands, the sagittal-plane orientation (θ) and center-of-pressure (CP) of F have been recently shown to covary such that the F lines-of-action pass near a point in space (intersection point, IP). The IP height (zIP) varies across the frequency bins being above the center-of-mass (CM) at frequencies below ~2 Hz and asymptotically approaching a sub-CM height at bands up to 6 Hz. This coordination pattern has been replicated with an optimal control simulation and shown to vary with conditions known to alter postural control. Young adult human volunteers (n=20, 19-35 years of age) without known neuromuscular deficits stood for 50 s for each of 14 conditions simulating the mechanics of wearing a headset and various levels of either vertical or horizontal field-of-view (FoV) restrictions. Results showed that an intermediate level of vertical and

horizontal FoV restrictions caused zIP to increase. The FoV restrictions that caused altered control of F are approximately the level of FoV restriction found in commonly used VRH. Furthermore, zIP increased with age across the span from 20-35 years for most conditions. These results provide evidence that control of standing posture preferentially utilizes peripheral vision, both vertical and horizontal. In all conditions participants had unobstructed central vision, but that was insufficient to allow participants to utilize the control observed without the headset. The presence of headset mass alone, without visual restriction, did not alter control. These observations emphasize the importance of peripheral vision for the control of standing balance, support the use of the IP metric to quantify control of standing balance, and urge caution when interpreting the results of VRH environments used for balance research.

Disclosures: K. Gruben: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Kreg Gruben. **J. Fox:** None. **J. Bartloff:** None.

Poster

PSTR031: Higher Order Control, Multi-Task Integration, and Theory of Posture and Gait

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Program #/Poster #: PSTR031.08/I3

Topic: E.06. Posture and Gait

Support: NIH NINDS Grant #1-R01-NS096083

Title: The effect of reward on preferred walking speed

Authors: *C. M. HEALY[1], A. A. AHMED[2];
[1]Univ. of Colorado, Boulder, CO; [2]Mechanical Engin., Univ. of Colorado, Boulder, CO

Abstract: Why do we run to greet a loved one but only walk to greet an acquaintance? Recent findings have shown that the speed at which we move reflects the value of what we hope to acquire. We reach faster and move our eyes faster to objects we value more; however, there is currently little understanding of how value influences self-selected walking speed. To probe the effect of reward on walking speed, we integrate a motion capture system, a self-paced treadmill, and a virtual reality (VR) headset to immerse subjects in a realistic environment. Subjects completed eight walking trials that required walking along a virtual path and collecting different amounts of rewards visualized as apples. Rewards were equally spaced 40 meters apart and varied between one, five, or ten apples. The distribution of rewards for a given trial were varied, where an environment may have a greater probability of a higher reward (Rich), or a greater probability of a low-value reward (Poor). For each trial, we measured the instantaneous walking speed. We hypothesized that preferred walking speed would *increase* with increasing value of the next immediately available reward. Eight subjects participated in this study (Age: 27.1±5.33 yrs; 2 Females). Preliminary results support our hypothesis: higher rewards were captured with greater walking speed (mean±s.e., five-apple: $\beta = 0.0784 \pm 0.0339$, $p = 0.0393$, ten-apple: $\beta =$

0.122 ± 0.0321, $p = 1.61 \times 10^{-4}$). We also find that subjects walked faster in the VR environment than the non-VR baseline trials (No VR: $\beta = -0.350 \pm 0.0467$, $p = 2.85 \times 10^{-10}$, No Reward+VR: $\beta = -0.211 \pm 0.0465$, $p = 2.63 \times 10^{-5}$). Collectively, our results suggest that walking vigor is modulated by reward value and a history of reward. These findings are a significant step in investigating vigor in walking and show promise that walking speed can provide a non-invasive marker of the implicit value the brain assigns the world around us.

Disclosures: C.M. Healy: None. **A.A. Ahmed:** None.

Poster

PSTR031: Higher Order Control, Multi-Task Integration, and Theory of Posture and Gait

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.09/I4

Topic: E.06. Posture and Gait

Support: NINDS R01NS096083
NSF GRFP

Title: The role of background effort on split-belt locomotion

Authors: *R. M. MARBAKER[1], A. AHMED[2];
[1]Paul M Rady Mechanical Engin., Univ. of Colorado Boulder, Boulder, CO; [2]Mechanical Engin., Univ. of Colorado, Boulder, CO

Abstract: Improving step length symmetry during split-belt adaptation is paralleled by decreasing metabolic cost (Finley et al. 2013). This improved efficiency may be an epiphenomenon of changing gait symmetry, but could energetic cost be driving motor adaptation?
We hypothesized that background effort could accelerate motor adaptation by increasing the urgency of initial learning and error reduction. Prior findings indicate that increasing reach effort via muscle co-contraction and walking effort via incline, both enhanced learning (Heald et al. 2018; Sombric et al. 2020). Alternatively, background effort could be an environmental factor that impairs motor adaptation, either by distraction or by reducing motivation.
We tested the effect of background effort in split-belt walking. In the split-belt task, participants (n = 45, 15 per group) walked on a treadmill with a 3:1 belt-speed ratio. Background effort conditions were differentiated by weight added to a vest worn by the participant (high effort = 15% body weight, medium = 5%, low = vest only). Participants were assigned to a single effort group and a baseline period was followed by learning, washout, and relearning. We assessed step asymmetry over the course of adaptation. Binned early and late learning and relearning metrics were compared between groups using ANOVAs. Asymmetry profiles were fitted with state space and exponential models.
We found no effect of background effort on split-belt adaptation In the split-belt walking study, participants' step lengths adjusted toward symmetry at the same rate (state space learning rates, p

= 0.52; exponential learning rate, p = 0. 24) and to the same extent (p = 0.13; late asymmetry). Participants also retained and relearned the rotation similarly. Asymmetry measures for step time, ground reaction forces, and step variability were also similar between effort conditions. We observed that background effort costs do not enhance or impair motor adaptation. This effort insensitivity could be applied in rehabilitation programs where resistance or effort could be added to movement rehabilitation to promote strength. The findings also serve as a foundation for investigation into the role of performance-dependent effort in learning.

Disclosures: R.M. Marbaker: None. **A. Ahmed:** None.

Poster

PSTR031: Higher Order Control, Multi-Task Integration, and Theory of Posture and Gait

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Support: NIH Grant NIA 1F31AG081129
NIH Grant R01 AG072756
NIH Grant R01 HD095975

Title: Effects of aging and cognitive-motor challenge on cortical motor contributions to standing balance control

Authors: *C. F. MASON[1], R. RASTOGI[5], R. RAJASHREE[2], C. GUZMAN[6], T. LEONE[2], K. WHITESIDES[2], S. EDAVALAPATI[3], J. SHAH[7], A. J. LOPEZ[4], M. R. BORICH[2,6], T. M. KESAR[2], L. H. TING[2,6];
[1]Neurosci. Grad. Program, Emory Univ., Decatur, GA; [2]Dept. of Rehabil. Med., [3]Neurosci. and Behavioral Biol. BS Program, [4]Neurol., Emory Univ., Atlanta, GA; [5]Northeastern Univ., Boston, MA; [6]Wallace H. Coulter Dept. of Biomed. Engin., Georgia Inst. of Technol. and Emory Univ., Atlanta, GA; [7]BS Program in Neurosci., Georgia Inst. of Technol., Atlanta, GA

Abstract: Cortical engagement in balance control is thought to increase with balance challenge, particularly as we age. Additionally, motor performance may degrade as cognitive resources are allocated away from balance, which leads to fall risk. We aim to characterize motor cortical contributions to corticospinal output during standing balance control in able-bodied young (YA) and older (OA) adults as balance and cognitive resource allocation are challenged. We hypothesize that hard balance tasks engage motor cortical mechanisms that are shared for hard cognitive tasks. We used transcranial magnetic stimulation (TMS) to measure corticospinal excitability (CSE) during easy (quiet stance; QS) and hard (narrow stance over foam; NS) standing tasks. To challenge cognitive-motor cortical resource allocation, easy (0-back) and hard (2-back) verbal working memory cognitive tasks were performed during each standing task. We predicted: 1) CSE is higher and cognitive-motor performance is lower during the challenging standing task; 2) CSE and cognitive-motor performance decrease during the hard vs easy NS

dual tasks (NS 2-back vs NS 0-back), since cognitive and motor areas compete for cortical resources; 3) OA show larger modulation of CSE with balance and cognitive challenge than YA due to greater reliance on cortical resources with aging. Data were collected in 18 YA (18-35 years, 9 male) and 18 OA (60-85 years, 9 male). CSE was assessed as the peak-to-peak amplitude of 20 motor evoked potentials (MEPs) elicited by TMS pulses targeted to the soleus hotspot. Cognitive-motor task performance was assessed with center of pressure (COP) sway, n-back accuracy, and n-back response times. Interim analysis revealed an effect of age and stance in CSE. Our analyses of effects of balance challenge on CSE showed that within the OA group, CSE was higher in NS (0.578 +/-0.284 mV MEP amplitude) vs QS (0.367 +/-0.214 mV), while YA showed no difference in CSE across stance. There were no differences in 2-back vs 0-back CSE across age groups or stance. COP sway and n-back error were higher during hard balance and cognitive tasks. Our preliminary results showed higher CSE during harder balance tasks in OA but not YA, indicating OA may recruit more corticomotor resources during challenging balance tasks. However, cognitive and dual task difficulty had no effect on CSE, suggesting verbal working memory areas may not modulate M1 during balance challenge. Alternatively, the tasks were not hard enough to challenge cortical resource allocation. This work will lay the foundation for developing neurophysiological biomarkers to predict falls risk, and precision (p)rehabilitation strategies to reduce falls.

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Poster

PSTR031: Higher Order Control, Multi-Task Integration, and Theory of Posture and Gait

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Program #/Poster #: PSTR031.11/I6

Topic: E.06. Posture and Gait

Support: NIH T32EB025816
NIH NICHD R01 HD095975

Title: Modulation of spinal excitability with balance task difficulty and cognitive dual task performance

Authors: ***C. GUZMAN**[1], C. F. MASON[2], T. M. KESAR[1,3], M. R. BORICH[1,3];
[1]Biomed. Engin., Georgia Inst. of Technol. and Emory Univ., Atlanta, GA; [2]Rehabil. Med., Emory Univ., Decatur, GA; [3]Physical Therapy, Emory Univ., Atlanta, GA

Abstract: Spinal reflex modulation is essential for balance control, with spinal excitability (SE) decreasing with age and postural demand. However, the neural control of balance can shift between spinal and cortical circuits. While cortical engagement during balance is thought to increase with age, concurrent cognitive task demands can compete for cortical resources,

compromising balance, and increasing falls risk. It is unclear how spinal reflex modulation is influenced by descending cortical signals when a cognitive task is performed concurrently with a balance task. We aim to quantify SE modulation across varying levels of balance and cognitive task difficulty in young (YA) and older (OA) adults.
We hypothesize that increased cognitive resource recruitment during balance challenge will modulate spinal excitability, particularly with age. We predict that 1) OA will show greater down-modulation of SE with increasing balance task difficulty compared to YA and 2) YA will show no modulation of SE and OA will show greater down-modulation of SE with increasing cognitive task difficulty.
SE was measured using peripheral nerve stimulation (PNS) during each cognitive-balance dual task condition. 6 YAs (18-35 years, 4 females) performed balance tasks of increasing difficulty (prone; quiet stance, QS; quiet stance on foam, QS foam; narrow stance on foam, NS foam). All balance conditions were performed concurrently with 0-back and 2-back verbal working memory tasks, and a no cognitive task control. SE was quantified as the peak-to-peak amplitude of 20 PNS-evoked soleus H-reflexes normalized to the maximal muscle response in each balance condition (H/Mmax). SE modulation was defined as the percent change in the average H/Mmax ratio of each condition compared to the prone and no cognitive task condition.
During the no cognitive task conditions, H/Mmax decreased from prone to QS (-48.11 ± 17.43%) but did not continue to decrease with increasing balance task difficulty (QS foam: -47.32 ± 22.44%; NS foam: -43.65 ± 17.06%). Across all cognitive task conditions, a two-way mixed effects ANOVA showed no main effects of stance ($p>0.05$), cognitive task difficulty ($p>0.05$), or interaction effects ($p>0.05$) on SE modulation.
Our preliminary results in YA show that while SE modulation occurred from prone to quiet standing, SE was not affected by standing balance task difficulty nor with the addition of a cognitive task. Ongoing work comparing YA and OA will elucidate the effects of aging and dual-task difficulty on spinal circuits, laying foundations for future studies to better understand and treat aging-related balance deficits.

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Poster

PSTR032: Sensori-Motor Transforms in Behavior

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Topic: F.01. Neuroethology

Support: NSERC RGPIN-2021-03180
DGECR-2021-00130

Title: The neurobiology of visually-guided ambush behavior in South American horned frogs (Ceratophrys)

Authors: *P. WU[1], D. B. LEITCH[2];
[1]Zoology, Univ. of British Columbia, Vancouver, BC, Canada; [2]Integrative Biol. and Physiol., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Frogs display diverse feeding behaviors with specific sensorimotor adaptations. While *Bufo* toads exhibit stereotyped prey-catching responses to simple moving cues, South American horned frogs (*Ceratophrys*) are voracious, sedentary ambush predators. We investigated unique predatory behaviors and associated visual system adaptations in Ceratophryids.
We videoed 11 adult frogs responding to visual stimuli, observing prey-catching movements to both live prey and simplified moving geometric stimuli. To functionally investigate the visual system, we used *in vivo* extracellular recordings in the optic tectum in 7 adult frogs. Their retinotopic map has prominent representation of superior, nasal fields, congruent with the forward-facing eye position within this genus. In response to visual cues, neurons were generally motion-sensitive to all stimuli but preferentially increased spiking to specific stimulus orientations. We identified at least three different classes of responses, tuned to different stimulus shapes and orientations.
Furthermore, we investigated behavior and responses to intra-specific moving visual cues. Cannibalism has been reported in several Ceratophryids species. Specifically, these frogs extend their hindlimbs in different configurations and patterns in a unique "luring" behavior, whose biological significance is not fully understood. We quantified frog predatory behaviors in response to different prey and found that orientation to conspecifics or frog videos were similar to those movements by insect prey. Hindlimb movement was preferentially performed when the frog was presented with a visible, live frog or frog video. We recorded neural responses to mealworm and frog luring video stimuli and found that individual neurons responding to worm videos also preferentially responded to frog-generated hindlimb movements. Collectively, these data suggest that the suite of predatory behaviors of Ceratophryids are mediated by specialized visual system adaptations. Moreover, frogs may exploit innate predatory responses and visual system adaptations to facilitate cannibalism.

Disclosures: P. Wu: None. **D.B. Leitch:** None.

Poster

PSTR032: Sensori-Motor Transforms in Behavior

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Support: Excellence in STEM Program Sanofi US Summer Research Award
Research as a High Impact Practice Grand Recipient
University of Scranton Neuroscience Research Award

Title: The telencephalon's influence on startle response plasticity in goldfish

Authors: *O. R. SANDER[1], M. GASPER[2], R. F. WALDECK[3];
[1]Neurosci. Program/Biology Dept., Univ. of Scranton, Scranton, PA; [2]Univ. of Scranton, Scranton, PA; [3]Biology/ Neurosci. Program, Univ. of Scranton, Scranton, PA

Abstract: Normally, goldfish make a quick C-shaped turn away from a vibratory stimulus known as an acoustic startle response. Prior research has shown that full ablation of the telencephalon significantly decreased the probability of a complete startle response, with a decreased turn angle of the C-turn (Collins & Waldeck, 2006). The startle response is mediated by the Mauthner cell (M-cell) located in the brainstem (Davis et. al., 1976; Korn and Faber, 1996; Hale et. al., 2016). The precise anatomical connection between the telencephalon and the M-cell circuitry is not yet understood. In this study, the lateral portion of the left lobe of the telencephalon was lesioned, and fish were tested for differences in turn angles before and after lesioning (n=9). Fish were also tested for a rescue response by a Dopamine D1 receptor agonist. Mean startle angle (MSA) was calculated. Lateral lesions significantly decreased the MSA. Following post-lesion testing, immersion in the Dopamine D1 agonist demonstrated a rescue effect, with a significant increase in the MSA ($p=0.0332265$). Acoustic startle responses were used as the stimulus, and trials were recorded and analyzed for three pre- and post- testing days. Statistical analysis revealed a significant difference between pre-testing and post-testing MSA ($p=0.0007444$). Medial lesion data was adapted from Opalka, 2017 to determine any significant difference between lateral and medial lesioning of the telencephalon. Results showed no statistical difference, but this may be because of the relatively small sample size. Future directions hope to include a larger sample size, show the tyrosine hydroxylase levels, and any and all projections from the telencephalon to the M-cell in the brainstem, which may reveal the precise dopaminergic involvement in the resulting modified startle response.

Disclosures: O.R. Sander: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Research as a High Impact Practice Grant Recipient; University of Scranton Neuroscience Research Award. Other; Excellence in STEM Program Sanofi US Summer Research Award. **M. Gasper:** None. **R.F. Waldeck:** None.

Poster

PSTR032: Sensori-Motor Transforms in Behavior

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Title: Neural mechanisms of behavioral variability and strategy selection in larval zebrafish

Authors: *V. WANG[1], A. B. CHEN[2], F. ENGERT[3];
[1]Harvard, Cambridge, MA; [2]Neurobio., Harvard Univ., Brookline, MA; [3]MCB, Harvard Univ., Cambridge, MA

Abstract: Survival in dynamic environments requires the ability to switch between exploiting an established action and exploring potentially better alternatives. This strategy switch consists of multiple processes: one that recognizes when the current behavior is no longer successful and abandons it in favor of exploration in action space, and another that promotes the maintenance of successful behavioral programs. Using larval zebrafish, we aim to understand the neural mechanisms underlying behavioral variability and the exploration versus exploitation of motor programs. Head-restrained, tail-free larval zebrafish exhibit a robust optomotor response to whole-field visual motion starting at around 6 days post fertilization. In closed loop virtual reality experiments, where swim bouts result in the expected visual flow, larval zebrafish generate stereotyped bouts of forward swimming. In open loop experiments, where tail oscillations do not affect the movement of the visual stimulus, we observe that fish exhibit increased variability in their swim bouts. We will use functional whole-brain imaging during this behavioral assay to characterize the neural circuits responsible for exploration of motor strategies. We extend this preparation to test strategy selection by allowing only a subset of swim bouts to drive visual feedback. We aim to identify brain-wide dynamics that encode exploration versus strategy selection. This will advance our understanding of action selection in different contexts and provide a mechanistic explanation for behavioral variability. Because identification of optimal motor strategies requires exploration of any organism's motor repertoire, these principles may suggest generalizable motifs across the animal kingdom.

Disclosures: V. Wang: None. **A.B. Chen:** None. **F. Engert:** None.

Poster

PSTR032: Sensori-Motor Transforms in Behavior

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Program #/Poster #: PSTR032.04/I10

Topic: F.01. Neuroethology

Support: R01 NS123887

Title: Identifying internal states underlying thermal navigation behavior in larval zebrafish using Hidden Markov models and in-vivo functional imaging

Authors: *K. BALAKRISHNAN[1], J. COSTABILE[1], M. HAESEMEYER[2];
[1]The Ohio State Univ., Columbus, OH; [2]Neurosci., The Ohio State Univ., Columbus, OH

Abstract: Animals exhibit sophisticated navigational behaviors to achieve various objectives such as foraging, thermoregulation, and exploration. For ectotherms, which lack inherent physiological mechanisms to regulate their body temperature, the modulation of internal temperature through behavioral navigation is vital for survival. Our investigation focuses on

elucidating the navigational strategies employed by the ectotherm vertebrate larval zebrafish through meticulous tracking of their movements within a controlled thermal gradient environment. By observing the discrete swimming bouts of larval zebrafish, we can deconstruct their behavior into distinct movement events, thereby facilitating the analysis of various bout-related parameters. These parameters encompass *bout distance*, *bout turn angles*, and *inter-bout intervals*, all of which vary according to the thermal environment of the fish. We have developed a model that elucidates how larval zebrafish integrate temperature cues to modulate their bout parameters. Previous studies had demonstrated that *bout distances* and *turn angles* increase with temperature, whereas *inter-bout intervals* decrease, suggesting an intuitive avoidance of extreme temperatures. However, the robust avoidance of cold temperatures warrants further investigation. Our analyses reveal an autocorrelation in consecutive bout distances and turn angles, suggesting the influence of longer-term control mechanisms on movement patterns. This implies the presence of distinct navigational strategies in response to varying temperature extremes. We model these differences using a combination of Hidden Markov Models, Generalized Linear Models and Gaussian Mixture Models (HMM-GLM-GMM) to delineate internal states governing turn angles in successive bouts. Our model identifies distinct states during thermal navigation, highlighting nuanced differences in navigation strategies between cold and hot temperature conditions. Specifically, our findings suggest a persistence of swim turns at lower temperatures, which diminishes at higher temperatures. Subsequently, leveraging in-vivo functional imaging via two-photon fluorescence microscopy, we identify neural correlates of temperature and its fluctuations. These neurons in the trigeminal ganglion and brainstem structures mimic model parameters. This corroborates the presence of internal states as described by the HMM, further enabling characterization of the neural circuits orchestrating downstream computations and fish behavior.

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Poster

PSTR032: Sensori-Motor Transforms in Behavior

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Topic: F.01. Neuroethology

Support: Israel Science Foundation grants 1684/20

Title: From representing movements to generating them: the low dimensional behavior of hunting zebrafish

Authors: ***Y. RUBINSTEIN**[1], M. MOSHKOVITZ[1], S. SHAPIRA[1], S. TIOMKIN[2], L. AVITAN[1];
[1]Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]San Jose State Univ., San Jose, CA

Abstract: Natural goal-directed behavior consists of a sequence of actions aimed at achieving a desired goal. Uncovering the underlying action selection principles requires a complete map of the entire repertoire of actions. Each action in this repertoire is manifested as a movement and leads to a consequence, which we term an outcome. The challenge of mapping the behavioral repertoire originates from the complexity of movements and the lack of comprehensive understanding of the corresponding outcomes. Therefore, quantifying both movements and outcomes will pave the way to understanding action selection principles.
Here we separately analysed actions selected during the zebrafish hunt from both outcome and movement perspectives. Focusing on outcomes, we show that outcomes repertoire is defined by two continuous parameters mixing distance and angles non-linearly. This subsequently uncovered underlying action selection principles. We then focused on movements, where the two-dimensional outcomes implied that movements are also two-dimensional. Indeed, we show that all possible movements can be fully generated using a two-dimensional control signal fed into a novel dynamical system. Finally, we combine the two perspectives and show how desired outcomes are translated into the full dynamics of the tail.
Together we show that zebrafish actions are fully defined by two parameters. This representation of actions suggests an efficient 2d neural representation of both movements and outcomes, and provides a mechanistic prediction for how the brain implements a selected action via motor movement.

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Poster

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Support: TUBITAK Grant 120E198

Title: The impact of sensory salience on tracking behavior in weakly electric fish

Authors: *C. S. OZDEMIR[1], E. AYDIN[1], I. UYANIK[2];
[1]Bioengineering Div., Hacettepe Univ., Ankara, Turkey; [2]Electrical and Electronics Engin., Hacettepe Univ., Ankara, Turkey

Abstract: This study explores the impact of sensory salience on the refuge tracking performance within two species of weakly electric fish: black ghost knifefish (*Apteronotus albifrons*) and glass knifefish (*Eigenmannia virescens*). Weakly electric fish are known for exhibiting shelter-seeking behaviors in nature, utilizing the force generated by their ribbon-like anal fins to maintain their position within the shelters when necessary. We designed and built an experimental setup that allows us to examine the inherent shelter-seeking behavior of these

species in the laboratory through a refuge tracking experiment. We conducted a series of behavioral experiments with individuals of these species inside a 3D-printed refuge whose movements are dictated by a computer-controlled system. The experimental conditions varied refuge length, illumination, structure, and conductivity levels. Various sensory salience levels were examined through 54 different conditions, with five individual fish tested for each species. Based on the time-domain root-mean-squared error (RMSE) and frequency-domain tracking error metrics, tracking performance appeared significantly influenced by refuge length and illumination, with species-specific variations. We also observed the effects of embedded windows within the refuge on tracking behavior, especially in darker conditions. These findings underline the key role of sensory salience in refuge tracking, necessitating further research on the exclusive sensory systems of each species.

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Poster

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Topic: F.01. Neuroethology

Support: NSF IOS-2203122
R25 NS130965-02

Title: Central coordination of signaling and swimming motor pathways

Authors: *M. STANFORD[1], M. FUKUTOMI[3], B. CARLSON[2];
[2]Biol., [1]Washington Univ. in St. Louis, St. Louis, MO; [3]Dept. of Biol., Washington Univ. In St. Louis, St. Louis, MO

Abstract: Weakly electric mormyrid fish offer a simplified model for understanding the coordination of complex behaviors. These fish use electric organ discharges (EODs) for communication and electrolocation, the mechanisms of which are well understood. EOD production is controlled by a central electromotor (EM) circuit, which has reciprocal connections with the optic tectum (OT). The OT, a homologue of the mammalian superior colliculus (SC), plays a key role in multimodal sensory processing and sensorimotor integration. Superficial regions of the OT/SC are responsive to visual input, whereas deep regions respond to multimodal sensory inputs. The OT/SC is a known mediator of visuomotor coordination; however, it is unclear how the OT integrates sensory input in fish with electrogenic capabilities to alter motor and/or electromotor output. Preliminary behavior experiments demonstrate that the rate of EOD production increases during swimming. Additionally, previous studies show that electrical stimulation of the OT in paralyzed fish evokes both fictive EOD production and fictive swimming, suggesting there are specific areas of the OT interacting with both the EM circuit and swim motor circuit. This study investigates the functional anatomy of the mormyrid OT and its

connections to the EM and swim circuits in *Brevimyrus niger*. To first understand regional variability of the OT, we applied a 10-pulse electrical stimulus (100 μA) at 16 different locations along a grid at depths of 50, 200, and 400 μm. Fictive EOD recordings were taken from electromotor neurons (EMNs) in the tail, and fictive movement recordings were obtained from myosepta dorsal to the lateral line and rostral to the dorsal fin. Stimulation could evoke multiple fictive EODs and a single burst of fictive movement, indicative of a singular tail bend. Across individuals, stimulation evoked increases in EOD rate with increasing OT depth while responses in superficial regions varied across individuals, with stimulation resulting in decreases, no change, or weak increases in EOD rate. We predicted that regions showing the greatest excitatory fictive EOD responses (400 μm) would also exhibit the most robust fictive swimming responses. At this depth, we applied a 100 Hz stimulation for five seconds. This stimulus evoked multiple fictive EODs and multiple, rhythmic bursts of fictive movement, indicative of swimming. Excitatory fictive EOD responses and movements were greatest in deep OT, where multimodal stimulus integration occurs, suggesting that deep OT is likely involved in coordinating movement and EOD output patterns during active sensing behavior.

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Poster

PSTR032: Sensori-Motor Transforms in Behavior

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Program #/Poster #: PSTR032.08/I14

Topic: F.01. Neuroethology

Support: TUBITAK 120E198

Title: Closed-loop control of locomotion: simultaneous encoding of sensory and premotor signals in midbrain neurons

Authors: *I. UYANIK[1], N. J. COWAN[2], E. S. FORTUNE[3];
[1]Hacettepe Univ., Ankara, Turkey; [2]Dept. of Mechanical Engin., Johns Hopkins Univ., Towson, MD; [3]New Jersey Inst. of Technol., Newark, NJ

Abstract: Closed-loop control systems use sensory feedback to modulate motor outputs. We measured neurophysiological activity (N=80 units) in the midbrains of freely swimming weakly electric fish (*Apteronotus leptorhynchus,* N=13) that performed an image stabilization task, refuge tracking. In refuge tracking fish exhibited smooth-pursuit (linear tracking, ‘exploit’) and active-sensing (nonlinear movements, ‘explore’) modes. In both modes, we found neurons that simultaneously encoded sensory feedback that occurred 50--200 ms earlier, and fish movement that occurred 50--200 ms after spiking activity. Sensory feedback was encoded as selectivity for combinations of velocity and acceleration of the relative movement of the fish and the refuge. Encoding of fish movement was manifest as correlations between neural activity and subsequent accelerations of the fish. Further, we observed an up to threefold increase in firing rates during

active sensing compared to smooth pursuit. These changes in firing rates were accompanied by shifts in selectivity for velocity and acceleration. The increase in firing rates and changes in selectivity may reflect differences in control policy associated with smooth pursuit and active sensing. Finally, a recent report suggests that switching between smooth-pursuit and active-sensing modes is driven by uncertainty in state estimation. We are investigating how uncertainty in state estimation is manifest in neurophysiological activity in midbrain neural circuits.

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Poster

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Topic: F.01. Neuroethology

Support: TUBITAK Grant 120E198

Title: A fish-in-the-loop comparison of various active sensing models

Authors: *E. Y. AYDIN[1], O. K. KARAGOZ[3], M. M. ANKARALI[3], A. DEMIREL[2], I. UYANIK[2,1];
[1]Bioengineering Div., [2]Dept. of Electrical and Electronics Engin., Hacettepe Univ., Ankara, Turkey; [3]Dept. of Electrical and Electronics Engin., Middle East Tech. Univ., Ankara, Turkey

Abstract: This study explores the underlying mechanism of active sensing, a phenomenon widely observed across various animal species that allows animals to enhance their environmental perception at the expense of additional energy. To date, the understanding of this mechanism still needs to be discovered. Most studies perceive active sensing as a continuous or intermittent bursts of noise signals. We, however, proposed an alternative theory in our previous study (Karagoz et al., 2024), suggesting active sensing is a closed-loop process, essentially, where animals self-initiate additional active sensing movements to improve their state estimation. To validate our theory, we developed a custom experimental setup that allows weakly electric fish to perform refuge-tracking behavior under various manipulations. Specifically, our system generates active sensing signals based on different models to stimulate the fish. The experimental setup includes a refuge attached to a linear actuator, providing visual and electrosensory stimuli for the fish. We experimented with N=5 *Eigenmannia virescens*, with a constant-frequency stimulus movement profile consisting of three frequencies (0.10, 0.15, 0.25 Hz). The experiments were repeated under different illumination levels (light and dark). Kinematic responses were recorded for five replicates under each condition. In addition to the experiments, we conducted simulations using Matlab to investigate further the effects of different models of active sensing generators. Observing how the fish enhanced their tracking abilities showed that active sensing could be a closed-loop process prompting animals to induce

purposeful movement adjustments, thereby improving their state-estimation capabilities consistent with their specific tasks.

Disclosures: E.Y. Aydin: None. **O.K. Karagoz:** None. **M.M. Ankarali:** None. **A. Demirel:** None. **I. Uyanik:** None.

Poster

PSTR032: Sensori-Motor Transforms in Behavior

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.10/

Topic: F.01. Neuroethology

Support: TÜSEB Grant 16548

Title: Investigation of the effects of sensory salience on target tracking performance of zebrafish during rheotaxis

Authors: *S. SOLMAZ[1], I. UYANIK[2];
[1]Bioengineering Div., Hacettepe Univ., Ankara, Turkey; [2]Electrical and Electronics Engin., Hacettepe Univ., Ankara, Turkey

Abstract: Animals rely on multisensory information to guide their behavior, and this is particularly evident in the case of *Danio rerio* (zebrafish). Zebrafish demonstrate a remarkable ability to track targets during rheotaxis, utilizing sensory inputs from various modalities. In previous research, we observed that zebrafish effectively track the trajectories of a D-shaped tube, which obstructs water flow, during their natural rheotactic behavior. In this study, we investigate how the quality of multisensory information effects zebrafish's tracking performance within a custom-designed swim tunnel. In our experiments, we employed a transparent D-shaped tube to obstruct water flow, providing mechanosensory cues to the fish. Additionally, we introduced a thinner red stick within the tube to generate simultaneous visual cues. This nested tube structure allowed us to provide both mechanosensory and visual stimuli for the fish to stimulate their target tracking behavior. To manipulate the salience of multisensory information, we made three key adjustments: (1) altering the illumination between light and dark, (2) maintaining or removing the outer transparent D-shaped tube, and (3) varying the diameter of the inner red stick. We conducted experiments with three zebrafish under each sensory condition, subjecting the tube to constant-frequency sinusoidal signals at different frequencies. By analyzing the tracking performance of the fish and estimating their frequency response to tube movements, we gained insights into the multisensory nature of zebrafish target tracking behavior during rheotaxis. Statistical analyses revealed a significant improvement in target tracking performance as the quality of multisensory information increased.

Disclosures: S. Solmaz: None. **I. Uyanik:** None.

Poster

PSTR032: Sensori-Motor Transforms in Behavior

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Topic: F.01. Neuroethology

Support: TUBITAK Grant 120E198

Title: Predictive uncertainty in state-estimation drives active sensing behavior

Authors: *O. KARAGOZ[1,2], A. KILIC[1,3], E. AYDIN[4], M. M. ANKARALI[1,2], I. UYANIK[5,4]; [1]Electrical and Electronics Engin., [2]Ctr. for Robotics and AI, Middle East Tech. Univ., Ankara, Turkey; [3]Biomed. Engin., Basel Univ., Basel, Switzerland; [4]Bioengineering, [5]Electrical and Electronics Engin., Hacettepe Univ., Ankara, Turkey

Abstract: The closed-loop interaction between sensory and motor systems in organisms determines how they perceive and respond to their environments. In this closed loop, while the central nervous system decides on motor actions using sensory feedback signals, the resulting motor movements naturally shape the sensory feedback signals received from the environment. If these motor movements serve a purpose, such as increasing sensory volume, focusing attention, or improving sensory feedback signals, they represent a form of behavior known as active sensing. Although active sensing is widely observed among animals, its behavioral and neural mechanisms still need to be understood. In this study, we focus on weakly electric fish to understand the mechanisms of active sensing. These fish prefer to hide inside small shelters in their habitat to avoid predators. Moreover, if these shelters start to move, the fish swim to follow the shelter's movements to remain hidden within them. Leveraging this natural behavior, we have developed a new experimental setup. Using a PVC shelter moved by a linear motor, we stimulate the fish's instinct to track the shelter. This single axis following behavior provides a unique environment for applying system identification methods to reveal the mechanism behind active sensing. As previous studies have shown, under light conditions, weakly electric fish can precisely follow the movements of the shelter using feedback from their visual and electro-sensory systems. In the darkness, however, they perform additional high-frequency active sensing movements while tracking. We hypothesize that these active sensing movements are performed to enhance the estimation performance of their state. To test our hypothesis, we created a simulation of the fish's musculoskeletal system and sensory model. Unlike previous studies, we modeled the active sensing generator as a closed-loop system that produces active sensing movements based on the predictive uncertainty of the stochastic closed-loop system model. This closed-loop process aims to select the optimal active sensing action that minimizes the predictive uncertainty of the next movement while considering energy cost and feasibility. Using refuge tracking data from N=3 fish, we validated the performance of our model. We demonstrate that the proposed model produces fish trajectories statistically indistinguishable from real fish. Additionally, we compare this closed-loop method with open-loop and quasi-open-loop methods, showing that the proposed predictive uncertainty-based active sensing model outperforms the other models in capturing the characteristics of the fish's response.

Disclosures: **O. Karagoz:** None. **A. Kilic:** None. **E. Aydin:** None. **M.M. Ankarali:** None. **I. Uyanik:** None.

Poster

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Topic: F.01. Neuroethology

Support: NIH K99-DC020770-01A1

Title: Prediction and Error in the Mouse Auditory Cortex

Authors: ***N. AUDETTE**[1], D. M. SCHNEIDER[2];
[1]New York Univ. Ctr. For Neural Sci., New York, NY; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Many of the sensations experienced by an organism are caused by their own actions, and accurately anticipating both the sensory features and timing of self-generated stimuli is crucial to a variety of behaviors. In the auditory cortex, neural responses to self-generated sounds exhibit frequency-specific suppression, suggesting that movement-based predictions may be implemented early in sensory processing. By training mice to make sound-generating forelimb movements, we recorded detailed neural responses while mice produced and experienced sounds that met or violated their expectations. We identified suppression of responses to self-generated sounds that was specific across multiple acoustic dimensions and to a precise position within the trained movement. Prediction-based suppression was concentrated in L2/3 and L5, where deviations from expectation also recruited a population of prediction-error neurons. Prediction error responses were short latency, stimulus-specific, and dependent on a learned sensory-motor expectation. Recording when expected sounds were omitted revealed expectation signals that were present across the cortical depth and peaked at the time of expected auditory feedback. Building on these findings, we are pursuing the substrate of prediction-based suppression by recording neural activity from identified cell types and auditory brain regions.

Disclosures: **N. Audette:** None. **D.M. Schneider:** None.

Poster

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Title: Cortical control of skilled, sound-guided behavior in mice

Authors: *G. W. ZEMPOLICH, D. M. SCHNEIDER;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Identifying mistakes is important for improving performance during acoustic behaviors like speech and musicianship. Although hearing is instrumental for monitoring and adapting these behaviors, the neural circuits that integrate motor, acoustic, and goal-related signals to detect errors and guide ongoing sensorimotor adaptation in mammals remain unidentified. Here, we develop a novel closed-loop, sound-guided behavior that requires mice to use real-time acoustic feedback to guide skilled ongoing forelimb movements. Large scale electrophysiology recordings reveal that the mouse auditory cortex integrates information about sound and movement, as well as encodes error- and learning-related signals during this sound-generating behavior. Distinct groups of auditory cortex neurons signal different error types, and the activity of these neurons predicts both within-trial and across-trial behavioral adaptations. Brief, behavior-triggered optogenetic suppression of auditory cortex during error signaling hinders behavioral corrections on both rapid and long time scales, indicating that cortical error signals are necessary for skilled acoustic behaviors. Together, these experiments identify a cortical role for detecting errors and learning from mistakes and suggest that the auditory cortex plays a critical role in skilled, sound-generating behavior in mammals.

Disclosures: G.W. Zempolich: None. **D.M. Schneider:** None.

Poster

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Support: Leon Levy Fellowship in Neuroscience, Leon Levy Foundation
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New York Stem Cell Foundation

Title: Multimodal activity of mouse auditory cortex during audio-visual-motor virtual reality

Authors: *A. LA CHIOMA[1], D. M. SCHNEIDER[2];
[1]New York Univ., New York, NY; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Auditory perception relies on predicting the acoustic consequences of our actions. The auditory cortex (AC) responds differently to expected versus unexpected self-generated sounds. Yet it remains untested whether AC dynamically updates predictions about self-generated sounds in a context-dependent manner.We developed a naturalistic audio-visual-motor virtual reality (VR) for head-fixed mice. Real-time locomotion tracking was performed to provide artificial footstep sounds that were yoked to a precise phase of the step cycle, creating an ethological and experimentally manipulable form of auditory reafference. While running on the treadmill, mice traversed two different contextual environments, each consisting of a distinct visual corridor accompanied by distinct footstep sounds. Using this system, we asked whether AC neural activity reflects predictions about the sound that footsteps are expected to produce in a given context, and to what extent contextual and motor signals integrate with auditory information.Following behavioral acclimation, we made high-density neuronal recordings from primary AC as mice traversed the two VR contexts and experienced expected or deviant footsteps. We observed overall suppression of neural responses to self-generated sounds compared to the same sounds heard passively. Subsets of neurons responded differently to the same sound heard in the expected versus the unexpected context. These expectation violation-like signals emerge immediately after entering a new context, suggesting a rapid updating of predictions. Population-level analysis indicates that context information is embedded in AC population activity. Our results suggest that AC combines auditory and motor signals with visual cues for context-dependent processing of self-generated sounds.

Disclosures: A. La Chioma: None. **D.M. Schneider:** None.

Poster

PSTR032: Sensori-Motor Transforms in Behavior

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Program #/Poster #: PSTR032.15/I20

Topic: F.01. Neuroethology

Title: Mice adapt their navigation behavior based on self-generated sounds and perceived predatory risk

Authors: *A. CORREDERA ASENSIO[1,2], R. E. PETERSON[3], A. LA CHIOMA[3], D. GARCIA[3], S. CHANG[3], D. M. SCHNEIDER[3];
[1]Neurosci., New York Univ., New York, NY; [2]Center for Neural Science, New York University, New York, NY; [3]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: In the wild, mice are a common prey species and display sophisticated behaviors to evade danger. They exhibit reactive behaviors such as freezing and fleeing in response to immediate threats, while also adopting proactive strategies to avoid threatening situations in the

first place, for instance, by traveling under canopy rather than out in the open. Previous studies indicate that wild mice and wild-caught mice show a preference for quiet over noisy surfaces, suggesting that mice might make navigational choices that minimize the noise they produce, thereby lowering the risk of predation. However, it remains unclear whether these behavioral strategies are innate or require experience with predators, and it is unknown whether mice adjust their behaviors as a function of perceived predatory risk. Here, we quantified the navigational choices of laboratory mice as they walked in an arena that produced different sounds in different locations. Although mice spend more time on a loud natural substrate (leaves) compared to a silent artificial surface (rubber), they also are more stationary on leaves, potentially to reduce the sound they generate. To isolate navigational strategies that are influenced by hearing, we built a virtual reality system in which mice walked on rubber and their locomotion sounds were under experimental control. The arena was divided in half, such that mice made self-generated sounds on one side but their movements were quiet on the other. Mice tend to avoid areas of virtual self-generated sounds but show less aversion to environmental sounds, suggesting that place preference behavior is governed in part by agency. Finally, we introduced multi-modal predatory cues and found that mice make strategic decisions that might be influenced by the acoustic consequences of their movements. Overall, our findings suggest that mice exhibit complex navigational behaviors influenced by the acoustic landscape, with implications for understanding their survival strategies in the face of predation.

Disclosures: **A. Corredera Asensio:** None. **R.E. Peterson:** None. **A. La Chioma:** None. **D. Garcia:** None. **S. Chang:** None. **D.M. Schneider:** None.

Poster

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Program #/Poster #: PSTR032.16/I21

Topic: F.01. Neuroethology

Support: NIH Grant 1R01-DC018802

Title: Learning within a sensory-motor circuit links action to expected outcome

Authors: *W. ZHOU[1], D. M. SCHNEIDER[2];
[1]New York Univ., New York, NY; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: The cortex integrates sound- and movement-related signals to predict the acoustic consequences of behavior and detect violations from expectations. Although expectation- and prediction-related activity has been observed in the auditory cortex of humans, monkeys, and mice during vocal and non-vocal acoustic behaviors, the specific cortical circuitry required for forming memories, recalling expectations, and making predictions remains unknown. By combining closed-loop behavior, electrophysiological recordings, longitudinal pharmacology, and targeted optogenetic circuit activation, we identify a cortical locus for the emergence of

expectation and error signals. Movement-related expectation signals and sound-related error signals emerge in parallel in the auditory cortex and are concentrated in largely distinct neurons, consistent with a compartmentalization of different prediction-related computations. On a trial-by-trial basis, expectation and error signals are correlated in auditory cortex, consistent with a local circuit implementation of an internal model. Silencing the auditory cortex during motor-sensory learning prevents the emergence of expectation signals and error signals, revealing the auditory cortex as a necessary node for learning to make predictions. Prediction-like signals can be experimentally induced in the auditory cortex, even in the absence of behavioral experience, by pairing optogenetic motor cortical activation with sound playback, indicating that cortical circuits are sufficient for movement-like predictive processing. Finally, motor-sensory experience realigns the manifold dimensions in which auditory cortical populations encode movement and sound, consistent with predictive processing. These findings show that prediction-related signals reshape auditory cortex dynamics during behavior and reveal a cortical locus for the emergence of expectation and error.

Disclosures: W. Zhou: None. **D.M. Schneider:** None.

Poster

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Topic: F.01. Neuroethology

Support: NIDCD R01DC018802-04
McKnight Foundation
New York Stem Cell Foundation

Title: Mouse motor cortex reflects movement, error and expectation of self-generated sounds

Authors: *A. M. KLINE, B. E. HOLEY, D. M. SCHNEIDER;
Ctr. For Neural Sci., New York Univ., New York, NY

Abstract: Many of the sensations we perceive are caused by our own actions, which we can distinguish from externally generated stimuli. In the auditory system, the ability to differentiate between external and self-generated sounds is crucial for vocal communication, musical training, and general auditory perception. The auditory system leverages the tight correlation between movements and the timing of incoming sensory information to discern whether a sound is self-generated, and through experience, animals form expectations for what each movement will sound like. Neural responses to expected self-generated sounds are suppressed in the primary auditory cortex (A1) and unexpected sounds elicit error-like responses. During sound-generating behaviors, the secondary motor cortex (M2) sends movement-related signals to A1 and is a potential source for establishing specific associations between sounds and their corresponding movements. Recent work suggests that M2 activity encodes a combination of movement-, sound-

, and expectation-related signals, yet it remains unknown how M2 activity changes with experience as mice learn and update auditory-motor expectations. Here, we test the hypothesis that corollary discharge signals sent from M2 to A1 do not simply encode action, but instead convey rich information to about movements and their expected acoustic consequences. To investigate motor cortical dynamics in response to expected and unexpected sounds, we trained mice to push a lever and receive a reward. At a reproducible time in the lever trajectory, a sound is played such that mice learn to associate it with their own movements. We show that M2 neurons reliably encode lever movements and also respond to unexpected self-generated sounds. Following extensive experience with a sound-generating lever, M2 responses to the expected self-generated sound become weak, but M2 retains the ability to respond to sounds that violate the mouse's expectation, suggesting that M2 neurons are sensitive to specific sensory outcomes. Ongoing two-photon calcium imaging experiments aim to understand how M2 ensembles change their activity as animals learn the acoustic consequences of their movements and how these ensembles reorganize when unexpected sounds are presented. These experiments will provide valuable insights into the brain's mechanisms for predicting and updating the acoustic consequences of our actions in real time and could uncover fundamental principles underlying dynamic information flow between sensory and motor regions of the brain.

Disclosures: **A.M. Kline:** None. **B.E. Holey:** None. **D.M. Schneider:** None.

Poster

PSTR032: Sensori-Motor Transforms in Behavior

Location: MCP Hall A

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Program #/Poster #: PSTR032.18/I23

Topic: F.01. Neuroethology

Title: Mouse Social Behavior is Influenced by Non-Vocal, Mouse-Produced Sounds

Authors: *D. GARCIA, A. CORREDERA ASENSIO, S. CHANG, D. M. SCHNEIDER; Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Mice vocalize during courtship and parental behavior, suggesting that real-time social behavior is influenced by acoustic cues. Many non-vocal behaviors also produce sounds, such as locomotion, digging, eating, and drinking. Recent work suggests that the acoustic landscape of socializing rodents is dominated by these non-vocal, rodent-produced sounds, yet it remains largely unknown whether or how non-vocal sounds influence social behavior. Here, we performed two experiments to explore how mouse social behavior changes when mice are noisy compared to when they are quiet. We first placed pairs of mice in adjacent linear tracks, the floors of which were covered with either noisy materials (leaves, bedding) or quiet materials (rubber). The linear tracks shared an opaque wall such that the mice could hear one another but could not see one another and we used markerless keypoint tracking (SLEAP) to quantify the behavior of both mice relative to one another. Over the course of tens of minutes, we observed a notable absence of vocalizations. Despite this lack of vocalizations, mice often synchronized

their locomotion, moving up and down their linear tracks in the same direction and at the same time, and often pausing their locomotion with synchrony that exceeded chance levels. Having observed synchrony with spatially separated mice, we next asked how freely interacting mice adjust their behavior on noisy surfaces and in the dark. In preliminary experiments, pairs of mice tend to occupy similar positions within an arena covered in dry leaves, suggesting that mice might use acoustic cues to locate social partners in the dark. Ongoing experiments and analyses are aimed at determining how auditory, tactile, and olfactory cues distinctly contribute to these synchronous social behaviors. Collectively, these experiments indicate that mouse social interactions change when mice are noisy, suggesting that non-vocal, mouse-generated sounds may play a role in naturalistic social interactions.

Disclosures: D. Garcia: None. **A. Corredera Asensio:** None. **S. Chang:** None. **D.M. Schneider:** None.

Poster

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Title: Localization of Cholecystokinin / Sulfakinin Neuropeptides in Biomphalaria glabrata, an Intermediate Host for Schistosomiasis

Authors: A. RIVERA[1], D. BRACHO-RINCON[2], ***M. MILLER**[3];
[1]Inst. of Neurobio., San Juan, PR; [2]Univ. of Puerto Rico, San Juan, PR; [3]Inst. Neurobio., San Juan, Puerto Rico

Abstract: Cholecystokinin (CCK) is one of the most ubiquitous neuropeptides in the mammalian brain, with proposed functions ranging from satiety and anxiety to learning and memory. Early reports of novel sulfated neuropeptides in insects, termed sulfakinins, noted shared features with the CCK carboxyl terminal and proposed their homology. Accumulating genomic data further supported the proposal that CCK-like signaling was present in the bilaterian common ancestor of protostomes and deuterostomes, leading to the designation of cholecystokinin / sulfakinin (CCK/SK). To date, little is known about the presence of authentic CCK/SK or its potential contributions to the well characterized neural circuits of gastropods. Using a neural transcriptomics approach (Mansour et al., 2017), we identified a transcript encoding a CCK/SK

neuropeptide in *Biomphalaria* (Bg-CCK/SK; pQGEWSYDYGLGGGRFa). This investigation examined Bg-CCK/SK expression in the nervous system and peripheral tissues of *B. glabrata*, a major intermediate host for the human trematode parasite *Schistosoma mansoni*. The Hybridization Chain Reaction (HCR) method was used to localize the *B. glabrata* CCK/SK transcript (*Bg-CCK/SK*) and CCK/SK-like immunoreactivity (CCK/SKli) was detected with a polyclonal (rabbit) antibody generated against pQGEWSYDYGLGGGRF-C. The largest numbers of CCK/SK expressing cells were in the visceral ganglion and the paired parietal ganglia. The cerebral and pedal ganglia contained fewer CCK/SKli neurons, and none were detected in the buccal or pleural ganglia. While the *Bg-CCK/SK* transcript was mainly confined to cell bodies, dense networks of CCK/SKli fibers coursed through all ganglia, commissures, and most peripheral nerves. There was general qualitative and quantitative agreement between transcript and peptide levels but there were instances where they diverged. CCK/SKli fiber systems were present on diverse peripheral tissues, including the mantle, kidney, lung, and penis sheath. The *Bg-CCK/SK* transcript was not detected in the periphery. Together, these observations support the pleiotropic role of a CCK/SK-related neuropeptide in *Biomphalaria*. Future studies will examine the impact of infection on Bg-CCK/SK expression at the levels of transcription and translation.

Disclosures: A. Rivera: None. **D. bracho-rincon:** None. **M. Miller:** None.

Poster

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Program #/Poster #: PSTR033.02/I25

Topic: F.01. Neuroethology

Title: The effect of temperature changes on the LGI-mediated tail flip response and neural circuitry

Authors: *J. KIM[1], *J. KIM[1], J. NADOLSKI[2], R. L. COOPER[3];
[1]Model Lab. Sch., Richmond, KY; [2]Benedictine Univ., Lisle, IL; [3]Dept. of Biol., Univ. of Kentucky, Lexington, KY

Abstract: Climate change is causing drastic temperature changes. Ectotherms are especially vulnerable because their external environments directly impact their internal body temperatures. Crayfish are common ectothermic models studied for their escape behavior and neural circuitry. A tap to the telson or abdomen can elicit a “tail flip.” Repeated stimulation, however, causes the crayfish to “habituate,” or significantly decrease excitability of the lateral giant axon. The habituation of the tail flip has not yet been studied in different temperatures but can be assessed for crayfish survival and invasiveness. For instance, a crayfish habituating quickly in the cold would not be very invasive because it could not respond to threats. In addition, there is limited research on the effect of temperature on neural circuitry, despite advancements in temperature-related therapies and conditions (e.g., therapeutic hyperthermia, organ preservation). To address

these questions, the study used animal models northern *Orconectes virilis* (North American crayfish) and southern invasive *Procambarus clarkii* (Red Swamp crayfish). Two experiments were performed, both after temperature changes from 21°C to 5°C or 30°C: (1) telson taps until habituation and (2) extracellular neural recordings. In Experiment 1, more *O. virilis* than *P. clarkii* survived in the cold, but *P. clarkii* were able to maintain their reflexes better in the warm. Experiment 2 revealed that in the cold, there was a general increase in activity; in the warm, a decrease. These results can be assessed to understand how climate change and temperature impact animal survival, invasiveness, escape behavior, and human health.

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Poster

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Title: Aeon: an open-source platform to study the neural basis of ethological behaviours over naturalistic timescales

Authors: *D. CAMPAGNER[1,2], J. BHAGAT[1], G. LOPES[3], L. CALCATERRA[1], J. AHN[4], A. ALMEIDA[3], F. J. CARVALHO[3], B. CRUZ[3], A. ERSKINE[3], C. LO[1], T. T. NGUYEN[4], A. POUGET[1], J. RAPELA[2], T. RYAN[3], J. REGGIANI[1], S. SWC FORAGING BEHAVIOUR WORKING GROUP[1,2];
[1]Sainsbury Wellcome Centre, UCL, London, United Kingdom; [2]GCNU, UCL, London, United Kingdom; [3]NeuroGEARS Ltd, London, United Kingdom; [4]DJ NEURO, Vathes LLC, Houston, TX

Abstract: The computations performed by brains are determined by the evolutionary pressures of survival and the behaviours they generate. Studying the neurobiology of ethological behaviours is important for advancing our knowledge of the brain because it provides a window into the function of neural circuits engaged in the computations they have evolved to do. Achieving this in a laboratory setting is challenging because of the need to mimic natural settings, including large and complex spatial environments, the presence of conspecifics and the ability to monitor long timescales, while retaining parametric control of key variables and rigorous measurement of behaviour and neural activity.
Here we developed AEON: a new platform for studying ethological behaviours and their neural basis in mice, continuously over time scales from weeks to months in a modular and scalable environment. The setup core is a modular arena where animals live, which can be programmed to mimic complex and dynamic environments where mice express social, defensive, drinking,

foraging and nesting behaviours. The arena is equipped with interactive elements like feeders,nesting areas, and a large array of sensors, including microphones, RFID readers, magnetic encoders, scales, and high-speed cameras, for continuously tracking animal position, pose and identity, and performing a deep, multidimensional quantification of mouse behaviours and internal state with millisecond resolution.
The AEON setup is complemented by a software suite for real-time data acquisition and control. Utilizing technologies such as Bonsai for task management, Harp for data synchronization, standardised python APIs for data preprocessing and analysis and DataJoint databases for data organisation, the platform ensures precise control, efficient collection of big data and a fully integrated end-to-end pipeline for data acquisition and analysis. We have also extended the functionality of Onix (OpenEphys) to operate in large arenas (> 2m diameter), therefore enabling large-scale long-term neuronal recordings in freely moving mice using Neuropixels probes continuously for days.
We demonstrate the platform's capability using experiments designed to probe the strategies that mice employ during a parametric digging-to-threshold foraging task, and how these adapt to rule changes and presence of conspecifics.
We believe that AEON is a significant advancement in the field of systems neuroscience, offering the tools to study natural behaviours and their neural correlates over prolonged periods, paving the way for a deeper understanding of the neurobiology that supports animal cognition.
DC, JB, GL, LC co-first authors

Disclosures: **D. Campagner:** None. **J. Bhagat:** None. **G. Lopes:** A. Employment/Salary (full or part-time):; NeuroGEARS Ltd. **L. Calcaterra:** None. **J. Ahn:** None. **A. Almeida:** A. Employment/Salary (full or part-time):; NeuroGEARS Ltd. **F.J. Carvalho:** A. Employment/Salary (full or part-time):; NeuroGEARS Ltd. **B. Cruz:** A. Employment/Salary (full or part-time):; NeuroGEARS Ltd. **A. Erskine:** A. Employment/Salary (full or part-time):; NeuroGEARS Ltd. **C. Lo:** None. **T.T. Nguyen:** None. **A. Pouget:** None. **J. Rapela:** None. **T. Ryan:** A. Employment/Salary (full or part-time):; NeuroGEARS Ltd. **J. Reggiani:** None. **S. SWC Foraging Behaviour Working Group:** None.

Poster

PSTR033: Sensory Motor Systems

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Support: NSF CRCNS 2113028

Title: How are variations in forces signaled and controlled? Hysteresis in force detection in the legs of insects and exploring its potential application in walking machines.

Authors: *S. ZILL[1], S. S. CHAUDHRY[1], I. KUDYBA[2], N. S. SZCZECINSKI[2];
[1]J.C. Edwards Sch. Med., Huntington, WV; [2]West Virginia Univ., Morgantown, WV

Abstract: Transient increases or decreases in forces can be significant in control of posture and walking. We have studied how variations in forces are encoded in the legs of insects. Sensory signals were recorded from the tibial campaniform sensilla, receptors that detect forces via cuticular strains. Forces were applied to the tibial segment of the hindlegs in juvenile (instars 7-11) and adult cockroaches, blowflies and stick insects. In all tests, the tibial sensilla respond vigorously to increases in bending forces applied to the leg. We also studied the effects of transient decreases in sensory discharges using waveforms that first rose exponential to a level. Sudden decreases (150 ms duration) were then applied after a stable level had been attained. Unexpectedly, sudden forces decreases produced transient complete inhibition of sensory firing at all force levels. Similar inhibition could be elicited in all stages of development in cockroaches. We are currently characterizing the effects of changes in the magnitude and rate of force decrease. We suggest that this hysteresis in sensory response (receptor stops firing) represents an adaptation in motor control: force signals can be components that aid in driving motor outputs. Many muscles in insects respond slowly and have residual muscle tensions. Complete inhibition of sensory firing could, therefore, contribute to more rapid adjustments of motor outputs to force variations. We have also developed a mathematical model of the receptor that can reproduce many characteristics of encoding seen in the animal and are currently testing the effects of transient perturbations in the model and in outputs of strain gauges in a robotic leg (located similar to the animal). Our results support the idea that hysteresis in sensory discharges may be advantageous in force control in both animals and walking machines.

Disclosures: S. Zill: None. **S.S. Chaudhry:** None. **I. Kudyba:** None. **N.S. Szczecinski:** None.

Poster

PSTR033: Sensory Motor Systems

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.05/I28

Topic: F.01. Neuroethology

Support: Swiss National Science Foundation
Deutsche Forschungsgemeinschaft

Title: Leaping in the dark: Visually guided navigation in nocturnal primates

Authors: *A. NOURIZONOZ[1], C. FICHTEL[2], D. HUBER[1];
[1]Basic Neurosciences, Univ. of Geneva, Geneve, Switzerland; [2]Behavioral Ecology and Sociobiology Unit, German Primate Ctr., Göttingen, Germany

Abstract: Vision, the key sensory modality for primates, plays an important role in navigation. In the case of nocturnal primates, such as the mouse lemurs, the visual system has evolved to adapt to low-light environments. Despite the darkness, mouse lemurs navigate through dense arboreal environments by leaping across tree branches. This behavior heavily relies on visual guidance to estimate the distance and landing target. How mouse lemurs perform these

impressive jumps in darkness, and how their ability to do so is affected by other environmental factors, remains an open question. To explore this matter, we used the latest version of the EthoLoop system (www.etholoop.org), an advanced real-time optical animal tracking system tailored for small nocturnal animals. This system not only tracks the spatial position of the animals with high temporal resolution (approximately 800 Hz) but also provides continuous, close-up views of their behavior in natural settings.
We will present how we set up a battery powered version of the EthoLoop system in the natural habitat of mouse lemurs in the deciduous dry forest on the east coast of Madagascar (Kirindy forest research station of the German Primate Center). For this purpose we developed a novel closed-loop jumping paradigm that involves multiple wireless and automated feeding platforms. These feeding platforms are strategically positioned to encourage the mouse lemurs to leap between natural tree branches, thereby reinforcing their natural jumping behavior in a reproducible manner, providing a rich dataset of the kinematics of individual jumps.
In parallel, we replicated these conditions in controlled laboratory settings, to study how mouse lemurs navigate and perform complex jumps under environmental conditions (such as illumination, visual contrast) which can be perfectly controlled. Finally, we complement these behavioral studies with wireless electrophysiology to investigate how volumetric space is represented in the primate brain while engaged in ethologically relevant behavior such as foraging. This dual approach not only deepens our understanding of the kinematics of their leaping behavior and how it differs between wild and captive environments, but also enables us to study neural activity under various environmental settings such as light conditions, providing a comprehensive view of their sensory-motor integration during navigation.

Disclosures: **A. Nourizonoz:** None. **C. Fichtel:** None. **D. Huber:** None.

Poster

PSTR033: Sensory Motor Systems

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.06/I29

Topic: F.01. Neuroethology

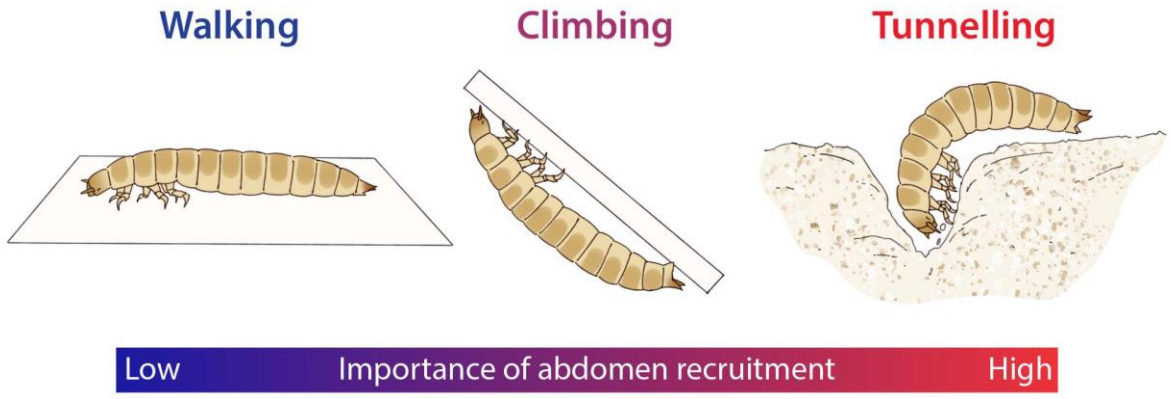
Support: Institute of Behavioural and Neural Sciences

Title: Context-specific coordination of movement in Tribolium castaneum larvae

Authors: *B. XU YING, M. F. ZWART, S. R. PULVER;
Sch. of Psychology and Neurosci., Univ. of St Andrews, St Andrews, United Kingdom

Abstract: Pest insects, like the flour beetle *Tribolium castaneum*, cause between 5-15% loss of stored grain products worldwide. Their success lies in their ability to adapt their movements to different environmental contexts. However, little is known about how their nervous systems coordinate adaptive movements. We employed videographic whole-animal and leg tracking to assess how late-instar *T. castaneum* larvae move over different terrain. We found they locomote

most efficiently over fibrous substrates (e.g. paper), consistent with their suggested original habitat of tree bark. Surprisingly, larvae could not crawl over flour and tunnelled upon contact, suggesting this is the main motor program in their current habitat. Unlike many hexapods, they use a bilaterally symmetric gait during fast locomotion, with movement propagating from segments T3 to T1. During slow locomotion, thoracic intra-segmental coordination is disrupted, while intersegmental coordination is largely preserved. Locomotion slows with progressive substrate inclination, and climbing overhangs requires leg movements and repeated planting of terminal abdominal structures (pygopods) into the substrate. Plant events do not significantly correlate with speed, but their onset coincided with swing starts, suggesting a stabilizing role. To probe the neural control of movement, we surgically severed the connective between thoracic and abdominal ganglia between A1 and A2. This led to escalating impairments in locomotion over flat terrain, climbing and tunnelling. General leg kinematic parameters were unaffected, confirming a stabilizing role for the abdomen. These results suggest that thoracic-abdominal coordination is required for effective movement and that larval gait and limb usage is context dependent. Our work provides the first kinematic analysis of *T. castaneum* larval locomotion and insights into its neural control. This work creates a foundation for future motor control studies in this genetically tractable insect that directly impacts global food security.



Disclosures: **B. Xu Ying:** None. **M.F. Zwart:** None. **S.R. Pulver:** None.

Poster

PSTR033: Sensory Motor Systems

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.07/I30

Topic: F.01. Neuroethology

Support: R34DA059723

Title: Dexterous food-sniffing: a unique form of multi-motor coordination for active sensing as mice feed

Authors: *M. GAO[1], J. M. BARRETT[1], M. BAID[1], D. W. WESSON[2], M. MA[3], G. M. SHEPHERD[1];
[1]Northwestern Univ., Chicago, IL; [2]Pharmacol. & Therapeut., Univ. OF FLORIDA, Gainesville, FL; [3]Neurosci., Univ. of Pennsylvania, Garnet Valley, PA

Abstract: Natural, ethologically critical behaviors often involve rapid orchestration of multiple body parts for coordinated complex actions. Food-handling is such a behavior, involving coordination of the hands and oral apparatus. In a recent study (Barrett et al., 2020, PLOS One) we found that mice, while handling food, briefly bring to the nares, appearing to take a single sniff. This “sniff maneuver” raises basic questions, including: during these single sniffs of hand-held food, are hand and head actions coordinated with breathing activity? How precisely, if at all, are “manual” sniff movements timed to coincide with an inspiratory breath? How does this type of “manually dexterous sniffing” compare to exploratory and other forms of sniffing? To begin to address these questions, we developed an approach based on multi-camera high-speed videography with computer vision controlled robotic camera, DeepLabCut-based kinematic tracking, intranasal measurement of breathing, electromyography of muscles involved in food-handling, and Miniscope recording of activity in cortical neurons. We used this system to analyze food-sniffing behavior in freely moving adult mice of both sexes.Analysis of the multi-modal data sets indicate a rich diversity of intricately coordinated activity across multiple phases of food-handling behavior, showing that mice dexterously sniff the food in their hands using a unique form of high-speed multi-motor-system coordination for active sensing. Key features of this complex behavior exhibit millisecond-scale temporal precision.

Disclosures: M. Gao: None. **J.M. Barrett:** None. **M. Baid:** None. **D.W. Wesson:** None. **M. Ma:** None. **G.M. Shepherd:** None.

Poster

PSTR033: Sensory Motor Systems

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.08/I31

Topic: F.01. Neuroethology

Support: NIH Grant 1R01NS121220

Title: A behavioral chain-sequencing mechanism: self-induced increased excitability of multifunctional serotonergic CPG neurons.

Authors: *E. HILL[1], W. N. FROST[2];
[1]Rosalind Franklin Univ., North Chicago, IL; [2]Chicago Med. Sch., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: How the nervous system orchestrates behavioral sequencing is the focus of study in a variety of species. Here we report a novel behavioral sequencing mechanism in the marine mollusk *Tritonia diomedea*. *Tritonia* escapes from predator contact via a stereotyped sequence - a rhythmic escape swim of several body flexion cycles followed by non-rhythmic rapid crawling lasting nearly an hour. The dorsal swim interneurons (DSIs) are serotonergic members of the *Tritonia* escape swim central pattern generator that drive both behaviors. Following their rhythmic firing during the escape swim they continue to fire tonically at an elevated rate for tens of minutes to drive post-swim crawling. What causes their post-swim elevated tonic firing? We show here that following the escape swim the DSIs exhibit an increase in excitability, as revealed by depolarizing constant current pulses, which lasts for nearly an hour. The duration of this effect matches the DSIs' post-swim elevated firing, as well as the duration of *Tritonia's* post-swim crawling behavior. We further found this increased excitability appears to be induced by the DSIs themselves. Driving a single DSI at 20 Hz for one minute leads to an increased excitability of the DSIs that lasts for several minutes. Our data are evidence for a model in which the firing of the DSIs during the swim self-induces an excitability change in the DSIs that becomes the engine that drives the next behavior in the sequence. This finding represents a simple and elegant neural chain mechanism that ensures that *Tritonia's* two escape behaviors are carried out in the proper sequence.

Disclosures: E. Hill: None. **W.N. Frost:** None.

Poster

PSTR033: Sensory Motor Systems

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NSF Grant IOS-2217657

Title: Allatotropin expression in the CNS of Biomphalaria glabrata, an intermediate host for human schistosomiasis

Authors: *D. NAZARIO[1], J. M. TORRES CRUZ[2], A. RIVERA[3], D. BRACHO-RINCON[4], L. C. VICENTE-RODRÍGUEZ[5], M. W. MILLER[6];
[1]Univ. of Puerto Rico, Caguas, Puerto Rico; [2]Univ. of Puerto Rico, Juncos, Puerto Rico; [3]Inst. of Neubiology, San Juan, PR; [4]Inst. of Neurobio., San Juan, Puerto Rico; [5]Dept of Anat. & Neurobio., UPR- Cayey, Cayey, Puerto Rico; [6]Inst. Neurobio., San Juan, Puerto Rico

Abstract: Schistosomiasis is a Neglected Tropical Disease (NTD) that affects approximately 240 million people globally, with over 90% of cases estimated to occur in Africa. The most widespread form of intestinal schistosomiasis is caused by the parasite *Schistosoma mansoni*. The life cycle of this trematode relies exclusively on freshwater snails from the genus *Biomphalaria* as its intermediate host. Within the snail, *S. mansoni* larvae multiply and transform into cercariae, the infectious form for humans. As infected snails undergo metabolic, behavioral, and physiological changes that support parasite development, we are exploring whether infection alters expression of regulatory neuropeptides. One potential neuropeptide target, designated *Biomphalaria* allatotropin (*Biom*-allato; GFRMNSASRVAHGYa), was identified using a neural transcriptomics approach (Mansour et al., 2017). As allatotropin-related peptides regulate feeding and reproduction in gastropods, the present study utilized two complementary histological techniques to localize its expression in the central nervous system (CNS) of *Biomphalaria glabrata*. The transcript encoding the *Biom*-allato precursor was localized using Hybridization Chain Reaction (HCR) *in situ* labeling and the neuropeptide was detected with an affinity purified antibody (rabbit, polyclonal) generated against C-GFRMNSASRVAHGY. Approximately 200 allatotropin-like immunoreactive (allato-li) neurons were distributed throughout the CNS. In the buccal ganglia, the localization of allato-li cells and the allatotropin transcript was well correlated. In other ganglia, co-localization of the mRNA and allato-li was less consistent. We propose that expression of the *Biom*-allatotropin peptide precursor is regulated at both the level of transcription and translation. Future investigation will test this hypothesis and examine whether schistosome infection alters the cellular expression pattern of *Biom*-allatotropin. This investigation may lead to novel strategies to disrupt the schistosome life cycle.

Disclosures: D. Nazario: None. **J.M. Torres Cruz:** None. **A. Rivera:** None. **D. bracho-rincon:** None. **L.C. Vicente-Rodríguez:** None. **M.W. Miller:** None.

Poster

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Program #/Poster #: PSTR033.10/I33

Topic: F.01. Neuroethology

Support: NIH R01: 1R01NS116595
NIH U01: 1U01NS131438

Title: Threshold based reflex strategies selection and role of indirect wing steering muscles on Drosophila's pitch control

Authors: *H. TEOH[1], A. LEUNG[1], B. LUDLOW[1], S. C. WHITEHEAD[2], E. EHRHARDT[3], M. H. DICKINSON[4], I. COHEN[5];
[1]Cornell Univ., Ithaca, NY; [2]Caltech, Pasadena, CA; [3]Inst. of Zoology, Univ. of Cologne,

Cologne, Germany; [4]Biol. and Bioengineering, Caltech, Pasadena, CA; [5]Cornell Univ. Col. of Arts and Sci., Ithaca, NY

Abstract: Flapping flight is an inherently unstable form of locomotion that requires insects such as Drosophila to constantly fine-tune their wing motion within milliseconds by coordinating a dozen pairs of wing-steering muscles. While past research has focused mainly on the direct wing steering muscles' impact on flight stability, little attention has been given to the role of indirect wing steering muscles. Our study investigates the influence of the dorsal tergopleural muscle, an indirect wing steering muscle, on the reflexive response for pitch stabilization through cellular manipulation within a free-flight behavioral assay. Our findings reveal that Drosophila employs a threshold-based approach in selecting pitch stabilization strategies. When facing minor disturbances inducing small angular velocities (less than approximately 1000 degrees per second) along the body pitch axis, the fly adjusts the extent of wing sweep to the front to generate corrective torques based on lift. However, for larger disturbances, we observe that the fly utilizes both lift and drag forces to produce more substantial corrective torques, incorporating an additional wing degree of freedom, the wing pitch angle. These results highlight a clear instance of threshold-based selection of reflexive strategies in behaviors that demand precise timing. Through photoinhibition experiments targeting the dorsal tergopleural muscle, we identify its crucial role in modulating the wing pitch angle during corrections to significant disturbances. Our findings not only refine the current simplistic framework for body pitch control by accounting for the interaction of multiple wing degrees of freedom but also shed light on the functional importance of the tergopleural muscle in flight, an aspect previously overlooked.

Disclosures: H. Teoh: None. **A. Leung:** None. **B. Ludlow:** None. **S.C. Whitehead:** None. **E. Ehrhardt:** None. **M.H. Dickinson:** None. **I. Cohen:** None.

Poster

PSTR033: Sensory Motor Systems

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Program #/Poster #: PSTR033.11/I34

Topic: F.01. Neuroethology

Support: NIH Grant 1R01NS116595
NIH Grant 1U01NS131438

Title: Optogenetic Stimulation of Haltere Basalar Muscles in Free Flight

Authors: *A. LEUNG[1], B. LUDLOW[1], H. TEOH[1], I. COHEN[2];
[1]Physics, Cornell Univ., Ithaca, NY; [2]Cornell Univ. Col. of Arts and Sci., Ithaca, NY

Abstract: Fruit flies have evolved the ability to execute a series of sophisticated aerial maneuvers in response to oncoming obstacles, such as gusts of wind, within milliseconds. To achieve fast and precise control of the wing muscles, the flight motor control system relies on

rapid mechanosensory feedback from the halteres. Halteres are a pair of dumbbell-shaped organs that oscillate at the same frequency as the wings and are thought to encode the angular velocity resulting from Coriolis forces acting on the fly's body during rotation. Additionally, previous studies have demonstrated that haltere muscles, which are analogous to the wing steering muscles, alter the phase spike timings of the wing muscles in tethered flies. However, the resulting wing kinematics from the manipulation of the haltere motor neurons in free flight remains unclear. To answer this question, we employed split Gal4 lines to target neurons innervating the haltere basalar muscles and optogenetically activated or silenced the muscles during free flight. Our initial findings reveal that bilateral activation of the haltere basalar muscles induces a pitch up response and an increase in wing stroke amplitude. Conversely, silencing these muscles results in a pitch down response and an overall decrease in wing stroke amplitude. This suggests that the haltere basalar muscles are essential in body pitch control and maintaining stable flight. Furthermore, unilateral silencing of the muscles produces a body roll maneuver, suggesting that the haltere basalar muscles may encode multiple degrees of freedom in flies. Additionally, prior studies have shown that haltere muscle activity is also modulated by visual perturbations. To further investigate the function of the haltere basalar muscles, we propose optogenetic activation or silencing during free flight in the presence of mechanical perturbations or visual perturbations as a different testing approach. This investigation will shed light on the intricate relationship between sensory inputs and motor control mechanisms mediated by the haltere basalar muscles.

Disclosures: **A. Leung:** None. **B. Ludlow:** None. **H. Teoh:** None. **I. Cohen:** None.

Poster

PSTR033: Sensory Motor Systems

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Program #/Poster #: PSTR033.12/I35

Topic: F.01. Neuroethology

Support: PAPIIT BG200424

Title: Two-interval beat production in the Rhesus monkey

Authors: *A. CASTILLO ALMAZÁN[1], L. PRADO[2], H. MERCHANT[3];
[1]Inst. de Neurobiología, Natl. Autonomous Univ. Mexico, Santiago de Querétaro, Mexico; [2]Inst. De Neurobiologia, UNAM, Campus Juriquill, Queretaro, Mexico; [3]Inst. de Neurobiologia UNAM, Queretaro, Mexico

Abstract: Two-interval beat production in the Rhesus monkey Ameyaltzin Castillo-Almazán, Luis Prado, Nori Jacoby & Hugo MerchantHumans have an amazing flexibility to perceive and synchronize with a large range of musical beats (Merchant&Honing 2014). In fact, during rhythm reproduction humans show a bias towards ratios of simple integers (1 to 4) (Jacoby&McDermott 2017); namely, a preference for simple beats such as the March (1:2) or the

Walz (1:3). Recently, it has been proposed that this ability is not human-specific, other species such as birds or cetaceans can synchronize to simple musical beats. (Patel2009, Cook2013). In addition, macaques can predictively entrain to isochronous metronomes (Gamez2018). Nevertheless, is still unknown whether monkeys can reproduce two interval beats and whether they show a preference for single integer ratios. Here, we trained two monkeys (*Maccaca mulata*) in a two-interval rhythmic tapping task where the animals were required to synchronize their taps to a sequence of two-interval rhythms defined by brief visual stimuli. We explored the flexibility of monkeys to reproduce rhythms within a wide range of ratios and total durations. We found that monkeys produced accurately and predictably large combinations of rhythms, synchronizing to long-short or short-long stimulus sequences in a flexible fashion. Together, the results support the notion that monkeys can perceive and synchronize to simple metric beats. References:•Cook, P. et al. (2013). A California Sea Lion (*Zalophus californianus*) Can Keep the Beat: Motor Entrainment to Rhythmic Auditory Stimuli in a Non Vocal Mimic. *Journal of Comparative Psychology*, 127, 4, 412–427. •Gamez, J. et al. (2018). Predictive rhythmic tapping to isochronous and tempo changing metronomes in the nonhuman primate. *Annals of the New York Academy of Sciences*, 1423,1, 396-414. •Jacoby & McDermott (2017). Integer Ratio Priors on Musical Rhythm Revealed Cross-culturally by Iterated Reproduction. *Current Biology*, 27, 1–12. •Merchant, H.&Honing, H. (2014). Are non-human primates capable of rhythmic entrainment? Evidence for the gradual audiomotor evolution hypothesis. *Frontiers in Neurosciences*, 7, 274, 1-8. •Patel, A.D. et al. (2009). Experimental Evidence for Synchronization to a Musical Beat in a Nonhuman Animal. *Current Biology*, 19, 827–830.

Disclosures: A. Castillo Almazán: None. **L. Prado:** None. **H. Merchant:** None.

Poster

PSTR033: Sensory Motor Systems

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Program #/Poster #: PSTR033.13/I36

Topic: F.01. Neuroethology

Support: NSF IOS 2042873
NIH 2R15GM125073-03

Title: Mommy Knows Best: Genetic and Circuit basis of female Drosophila decision making

Authors: *N. DHUNGANA[1], Y. LEE[2], D. SITARAMAN[3];
[1]California State University- East Bay, Hayward, CA; [2]California State University, East Bay, Hayward, CA; [3]Psychology, California State Univ. East Bay, hayward, CA

Abstract: Decision making processes dictate the lives of every living organism. The core of decision making is to select the best choice considering multiple factors including preference and consequences. Even the simplest organisms make decisions in their natural environment and studying these in animals with reduced complexity and increased accessibility can provide

critical insights into how the nervous system underlies this process. Here, we propose to use the fruit fly Drosophila melanogaster, as a system to understand the neural circuit mechanisms underlying decision making by studying the effects of neuronal and genetic manipulation on egg laying site selection or oviposition. Preliminary experiments show that female flies prefer to lay eggs on protein-rich non-fermenting yeast and avoid laying eggs on pure sugar substrates that attract predators. However, in their natural environment, flies do not encounter pure sugar or yeast and must sample combinations. As a first step in characterizing the decision-making process in egg laying preference behavior, we presented female flies with different substrates with various concentrations of yeast protein and sugar. We found that although yeast and sugar are favored nutritional sources, the female flies avoid laying eggs on sugar-yeast combinations which shows their aversion towards sugar over preference towards yeast. To investigate the circuit basis of decision making we systematically inhibited input, outputs and core processing regions of the mushroom body, a structure implicated in associative learning and other decision-making tasks and assayed oviposition preferences. We also screened the role of sugar and amino acid taste receptors in this choice behavior and found that Gr6f, 6e/d play a critical role in oviposition preference. Further, several Mushroom body output neurons (MBON1, MBON4 and MBON 9) are involved in decision making and relay these signals to oviposition command neurons (specifically pC1 and oviINs). Taken together, we have developed a novel decision-making task and mapped sensory, central processes and pre-motor circuits underlying these processes. We will present these data and additional hypotheses related to how sensory processes change as a function of mating and influence egg laying decision making.

Disclosures: **N. Dhungana:** None. **Y. Lee:** None. **D. Sitaraman:** None.

Poster

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Topic: F.01. Neuroethology

Support: NSF GRFP Grant DGE-2139899
NIH Grant 4R01NS116595-02
NIH Grant 1U01NS131438

Title: Characterization of three flight steering muscles used for robust roll control in freely flying drosophila

Authors: ***B. K. LUDLOW**[1], H. TEOH[2], A. LEUNG[2], S. C. WHITEHEAD[2], E. EHRHARDT[3], I. COHEN[2];
[1]Physics, Cornell Univ., Ithaca, NY; [2]Cornell Univ., Ithaca, NY; [3]Inst. of Zoology, Univ. of Cologne, Cologne, Germany

Abstract: Flapping flight is an inherently dynamically unstable endeavor, and is particularly challenging for small organisms. Despite these challenges and the often unpredictable environment in which they navigate, insects such as the fruit fly perform remarkable feats of aerial maneuverability and maintain their stability on timescales of mere milliseconds. Here, we focus on roll since it is the fly's most unstable degree of freedom, and elucidating the neuromuscular basis of its control provides significant insights into implementing fast motor control more broadly. We selected three steering muscles, i1, i2, and b3, which were implicated previously in roll control in tethered preparations, and share common inputs from haltere sensory afferents. We assessed their function in free flight by manipulating their corresponding motor neurons with optogenetic activation and silencing, chronic silencing, and magnetically-induced mid-flight mechanical perturbations. We compared our results to existing empirical models of roll stability, as well as a model-free approach to broadly understand their effect on roll control. Our experiments and simulations indicate that while unilateral activation of any one of these motor neurons is sufficient to drive roll steering maneuvers and corrective responses, flies are able to maintain roll stability and correct for mid flight perturbations even when one of these neurons are bilaterally silenced, with only subtle changes to their wing kinematics when compared with control flies. These results suggest that the control architecture for roll stability may contain multiple redundancies, in order to maintain stable flight even in the case of muscular damage or fatigue.

Disclosures: B.K. Ludlow: None. **H. Teoh:** None. **A. Leung:** None. **S.C. Whitehead:** None. **E. Ehrhardt:** None. **I. Cohen:** None.

Poster

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Program #/Poster #: PSTR033.15/I38

Topic: F.01. Neuroethology

Support: NIH Grant 5R01DC014989-08

Title: Characterization of neuronal responses across the auditory-motor system of primates using high-density Neuropixels probes

Authors: *S. BAUMANN[1], S. OGUNTAYO[1], P. A. WIKMAN[2], R. SAUNDERS[3], J. P. RAUSCHECKER[1];
[1]Dept. of Neurosci., Georgetown Univ., Washington, DC; [2]Dept. of Psychology and Logopedics, Univ. of Helsinki, Helsinki, Finland; [3]NIMH, McHenry, MD

Abstract: The primate auditory-motor system is a network of auditory, motor, parietal and subcortical regions that form a sensory-motor feedback loop. The network is crucial for the development and maintenance of human speech and music performance, but the system is also relevant for the control of nonhuman primate vocalizations and auditory-guided actions

(Rauschecker, 2011). Data from neuroimaging studies have provided evidence for interaction in a number of brain regions during speech and music performance in humans, and we previously highlighted the same network in rhesus macaques during a task requiring the reproduction of tone sequences using levers ('monkey piano'; Archakov et al. 2020). However, neuroimaging data do not have the temporal and spatial resolution to follow the neuronal interaction patterns between the involved brain areas. Here we present neurophysiological data that have been recorded using multiple, high-density Neuropixels probes across the auditory-motor network in rhesus macaques. The probes allow the monitoring of sensory-motor responses in a large number of neurons (typically 50-150 per probe) across the auditory-motor network. Three rhesus macaques were trained to listen to and reproduce seven tone sequences on a monkey piano (see above). Specific catch trials were infrequently interspersed in the tasks, such as key presses that result in no sound or the wrong sound, in order to provoke error responses. Recording chambers were implanted over the left hemisphere giving access to the premotor cortex (PMC), the auditory cortex (AC), the posterior parietal cortex (PPC), and the putamen of the basal ganglia (BG) for up to four probes at a time. We are recording from these areas based on our fMRI data (Archakov et al. 2020) while the animals perform the above auditory-motor tasks using nonhuman primate versions of semi-conductor (CMOS) based Neuropixels probes with a 45-mm shank length providing 384 channels per probe that are selectable from 4000 recording sites in double rows along the length of the probes. For each probe, the recording sites are from portions of the probe in one or several auditory-motor areas (e.g., PMC and putamen) based on prior MRI data and pilot probe mapping. From the probes, we are obtaining single-cell data (spike-sorted with kilosort3) with a particular focus on sensory-motor and error responses and local field potentials (LFPs) for network interaction analysis based on Granger Causality, in order to generate a network interaction model.

Disclosures: S. Baumann: None. **S. Oguntayo:** None. **P.A. Wikman:** None. **R. Saunders:** None. **J.P. Rauschecker:** None.

Poster

PSTR033: Sensory Motor Systems

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Topic: F.01. Neuroethology

Support: GR505140

Title: Sex differences in context-dependent persistent behavioral states in C. elegans

Authors: *C. BAINBRIDGE[1], G. REILLY[2], J. WANG[3], D. S. PORTMAN[4];
[1]Univ. of Rochester, Rochester, NY; [2]Neurosci. Grad. Program, Univ. of Rochester, Rochester, NY; [3]Neurosci., Univ. of Rochester Sch. of Med. and Dent., Rochester, NY; [4]Dept. of Biomed. Genet., Univ. of Rochester, Rochester, NY

Abstract: Animals must constantly integrate external sensory cues with internal-state information to optimally select adaptive behavioral strategies. Often these strategies are context-dependent such that an animal can flexibly shift between behavioral states to increase fitness. Because nutritional requirements and reproductive strategies often differ by sex, selection of adaptive behavioral strategies can be sexually dimorphic. However, the mechanisms by which biological sex impinges on underlying neuronal circuit logic to orchestrate flexible behaviors remains poorly understood. Previous work from our lab and others indicates that *C. elegans* exhibit sexually dimorphic neuronal responses and behavioral strategies. Here, we investigate sex differences in behavioral strategies by profiling features of locomotion between males and hermaphrodites under three distinct contexts. We do this by recording animals off-food, during immediate food encounter, and after prolonged starvation and re-feeding. Using a machine learning and behavioral analysis approach, we compared behavioral strategies between sexes under these three contexts. Preliminary results indicate sex differences in behavioral strategies between males and hermaphrodites in the absence of food both in the short-term and after nutrient stress. After food removal, only males persist in a restrictive search state. Similarly, after prolonged nutrient stress, we found that only hermaphrodites exhibit an increase in exploration. Surprisingly, we found remarkably similar behavioral strategies upon immediate food encounter and following re-feeding after nutrient stress. These data indicate context-dependent regulation of shared behavioral circuits in a sex-specific manner. Our approach provides an opportunity to explore mechanisms by which context-dependent modulation of circuit logic brings about flexible behavioral strategies.

Disclosures: C. Bainbridge: None. **G. Reilly:** None. **J. Wang:** None. **D.S. Portman:** None.

Poster

PSTR033: Sensory Motor Systems

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.17/I40

Topic: F.01. Neuroethology

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Title: Neurogenetic Mechanisms for Vocal Learning, Practice, and Performance

Authors: *M. FARIAS-VIRGENS[1], A. GUHA[2], K. OKANOYA[3], T. W. DEACON[4], X. XIAO[5], S. A. WHITE[6];
[1]Univ. of Washington, Seattle, WA; [2]UCLA, Los Angeles, CA; [3]Dept. of Life Sci., Grad. Sch. of Arts and Sci., The Univ. of Tokyo, Tokyo, Japan; [4]Anthrop., U C Berkeley, Berkeley, CA; [5]Univ. of California Los Angeles, LOS ANGELES, CA; [6]Integrative Biol. & Physiol., UCLA, Los Angeles, CA

Abstract: Learning skilled motor behaviors relies on iterative experimentation and performance evaluation. In this process, individuals adapt their behavior to maximize future rewards, such as aiming for successful prosocial interactions. Both the generation of variability in motor gestures and the reinforcement learning of motor programs leading to improved performance are supported by cortico-basal ganglia circuits. These principles set the basis for vocal production learning, a trait humans and songbirds share. Here, we identify transcriptomic patterns that distinguish a striatal region dedicated to song learning known as Area X from the more generalist striato-pallidum region ventral to it (VSP) in juvenile Bengalese finches (BF; *Lonchura striata domestica*). We find patterns of co-expression in juvenile BFs at the critical period of vocal plasticity and interrogate their preservation in adult BFs past that learning phase. We extend the analysis from within our adult BF cohort and compare Area X transcriptomes collected in two natural social contexts known to elicit differences in song stereotypy: singing alone versus to females. Results from our study corroborate and extend previous findings on the developmental and behavioral regulation of the expression of key genes coding for protein products highly enriched in striatal neurons signaling through the inhibitory neurotransmitter gamma-aminobutyric acid, termed medium spiny neurons. These genes' products play crucial roles in dopamine (DA) neuromodulation of arousal states and resulting behaviors and are deeply involved in the molecular etiology of Parkinsons' disease (e.g., FOXP1, FOXP2, FMR1, SNCA, SNCAIP, PRKN, and DA receptors). We observed that those genes' co-expression during song practice is highly preserved across the striatum of juvenile BFs, restricted to Area X in adults, and disassociated during performance to females. Additionally, our findings point to more dynamic patterns of expression of DA receptors in Area X than found in the surrounding striatum, where different DA receptor types instead show correlated expression to each other. These findings further highlight Area X's distinct functional specialization within the songbird basal ganglia and open avenues of inquiry on the molecular etiology of Parkinsons' disease.

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Poster

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Program #/Poster #: PSTR033.18/J1

Topic: F.01. Neuroethology

Support: NIH Grant R01NS122830

Title: Thermal gradient test for in vivo assessment of pain in rodents

Authors: *T. DEAKIN, S. WEI, R. E. RHOADES, T. TILLMAN, P. TANG, Y. XU;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Classical pain evaluation in rodents, such as the Hargreaves test for thermal hypersensitivity, heavily relies on an animal's reflexive response to a noxious stimulus. These threshold tests require intrusive human interactions with the animals and the quality of the data varies dependent on researcher experience due to supraspinal reflexes being misinterpreted as pain. We have engineered a thermal gradient device using a ½" thick aluminum plate with two Peltier heating and cooling units attached at each end with optimal thermal contacts. Four 137-cm long and 10-cm wide corridors divided by 10" black plastic walls allow four animals to simultaneously roam along the surface of the aluminum. The Peltier units create a linear thermal gradient from ~4°C to ~58°C along the aluminum surface. As the animals experience this variable thermal stimulus, we collect and process the position data with the video recording and analysis software AnyMaze. Utilizing a 30 second sliding window analysis of distance traveled (activity level), we found that the most robust data were collected between 30 and 600 seconds without interference from initial exploratory behavior. Data analysis of thermal preference (TP), as indicated by mean location selection along the thermal gradient, and thermal sensitivity (TS), as indicated by standard deviation of location selection, are used to differentiate among experimental groups based on student t-test analysis of thermal preference and thermal sensitivity. Repeated measure mixed design two-way ANOVA analysis of position data allowed us to identify interactions between thermal preference and animal's pain conditions. After data collection, the arena was split into 14 four-degree Celsius temperature zones and comparisons were made between measures using a Bonferroni post-*hoc* analysis. Quantified thermal preference and thermal sensitivity data can be used to differentiate between multiple variables. Sex differences in response to thermal stimuli clearly show that male C57BL/6J mice have a higher tolerance to cold temperatures than female littermates. CFA-induced inflammatory pain increases thermal sensitivity and induces symptoms of cold allodynia when compared to baseline measures. Treatment of CFA pain with morphine show not only a higher distance traveled but also a significantly higher tolerance to low temperatures regardless of pain condition. A noninvasive high-throughput test of quantifiable behaviors, as reported here, allows pain states and treatment efficacies to be evaluated with a higher degree of confidence. Removing researcher subjectivity allows for fast and reliable discovery of novel analgesics.

Disclosures: T. Deakin: None. **S. Wei:** None. **R.E. Rhoades:** None. **T. Tillman:** None. **P. Tang:** None. **Y. Xu:** None.

Poster

PSTR033: Sensory Motor Systems

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Program #/Poster #: PSTR033.19/J2

Topic: F.01. Neuroethology

Support: NSF Grant 1457291
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Alfred P Sloan Foundation

Title: Neuroanatomical variation between service and nonworking dogs

Authors: *S. GANESHRAM[1], S. BARTON[2], E. E. HECHT[3];
[1]Harvard Univ., Cambridge, MA; [2]Human Evolutionary Biol., Harvard Univ., Cambridge, MA; [3]Dept. of Human Evolutionary Biol., Harvard Univ., Cambridge, MA

Abstract: Not only do dogs exist as companions, but they also take on important roles as working assistants. One of these roles is service work, where a dog assists a disabled individual in their activities of daily living. Service dogs are not only trained for their roles but often come from programs that have selectively bred for desirable qualities over generations. Thus, the study aims to analyze what, if any, behavioral and neuroanatomical variation exists between service and nonworking companion dogs. Brains of Labrador retrievers (n = 33) from service and companion backgrounds were scanned using Magnetic Resonance Imaging. Owner-reported survey data on the dogs' behavior from the Canine Behavioral Assessment & Research Questionnaire (C-BARQ), a survey that measures dog temperament, was statistically analyzed using one-way ANOVAs to determine behavioral variation between the groups. Service dogs had significantly lower scores in attachment and attention-seeking ($p = 0.013$, 95% C.I. = [-2.150, -0.241]) and excitability factors ($p = 0.010$, 95% C.I. = [-1.923, -0.2450]) compared to control dogs. There was no significant difference in trainability scores between the two groups. Moreover, significant variation in brain regions between working groups potentially associated with working function was elucidated through voxel-based morphometry (VBM). Control dogs had expansion in the right marginal gyrus in comparison to service dogs. Service dogs had expansion in several regions in comparison to control dogs including, the olfactory bulb, ventromedial prefrontal cortex, prorean gyrus, ventral striatum, piriform cortex, anterior sylvian gyrus, cingulate, posterior ventral occipital lobe, thalamus, and cerebellum. Together, these results indicate significant neuroanatomical variation between service and companion dogs and raise implications regarding the impact of both behavioral selection and training on the canine brain.

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Poster

PSTR033: Sensory Motor Systems

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.20/J3

Topic: F.01. Neuroethology

Title: Incisor innervation and neuromuscular control of lower incisor movements in naked mole-rats (Heterocephalus glaber)

Authors: L. ECHOLS[1], N. J. VON KEYSERLING[2], *D. K. SARKO[3];
[1]Southern Illinois Univ., Carbondale, IL; [2]Neurosci., Washington Univ. Sch. of Med., St. Louis, MO; [3]Biomed. Sci., Div. of Anat. & Neurobio., Southern Illinois Univ., Sch. of Med., Carbondale, IL

Abstract: Naked mole-rats (*Heterocephalus glaber*) utilize their prominent incisors for important behaviors such as digging and exploring through tunnels in their subterranean habitat; grooming; play or defense behaviors such as incisor fencing; and transporting young. Compared to the upper incisors, which are fixed in place in the maxilla, the lower incisors are unusual in that they can be moved independently due to a flexible mandibular symphysis. This very likely generates greater proprioceptive and tactile cues related to the lower incisors, which would presumably require increased innervation compared to the upper incisors in order to transmit more tactile information to the central nervous system. Previous studies have noted that naked mole-rats can move their lower incisors laterally or rostrally, though little is known about the neuromuscular control of these movements. A study by our lab, Cain et al. (2019), conducted detailed postmortem dissections of neck muscle sizes and attachment sites and identified five main muscles that may contribute to the independent movement of the lower incisors in naked mole-rats. Cain et al. hypothesized the following for each lower incisor/hemimandible: the platysma myoides and mylohyoid facilitate lateral movements; the anterior digastric, geniohyoid, and mylohyoid control rostral movements; and the transverse mandibular muscle repositions the hemi-mandibles back to midline. In the current study, we conducted electrical stimulation of each target muscle in order to test these hypotheses. Due to their motility, we hypothesized that the lower incisors have more robust innervation supporting more pronounced sensorimotor control compared to the upper incisors. To examine this, we quantified axonal innervation using electron microscopy techniques. Our findings indicate that stimulation of the anterior digastric and transverse mandibular muscles induced lateral movement of the lower incisors. Regarding innervation, the superior alveolar nerve supplying the upper incisor has ~1,000 axons. In contrast, the inferior alveolar nerve supplying the lower incisor has ~3,500 axons. Naked mole-rats, at less than 1/7th the body mass of rats, have a comparable number of axons in their inferior alveolar nerves. This indicates a high degree of lower incisor innervation for their body size and greater orofacial sensorimotor control. Future studies will expand upon this unique evolutionary adaptation by testing additional groups of muscles to elucidate which muscles control rostral movements of the lower incisors, including ICMS of motor cortex to elicit tooth movements.

Disclosures: L. Echols: None. **N.J. von Keyserling:** None. **D.K. Sarko:** None.

Poster

PSTR033: Sensory Motor Systems

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Program #/Poster #: PSTR033.21/J4

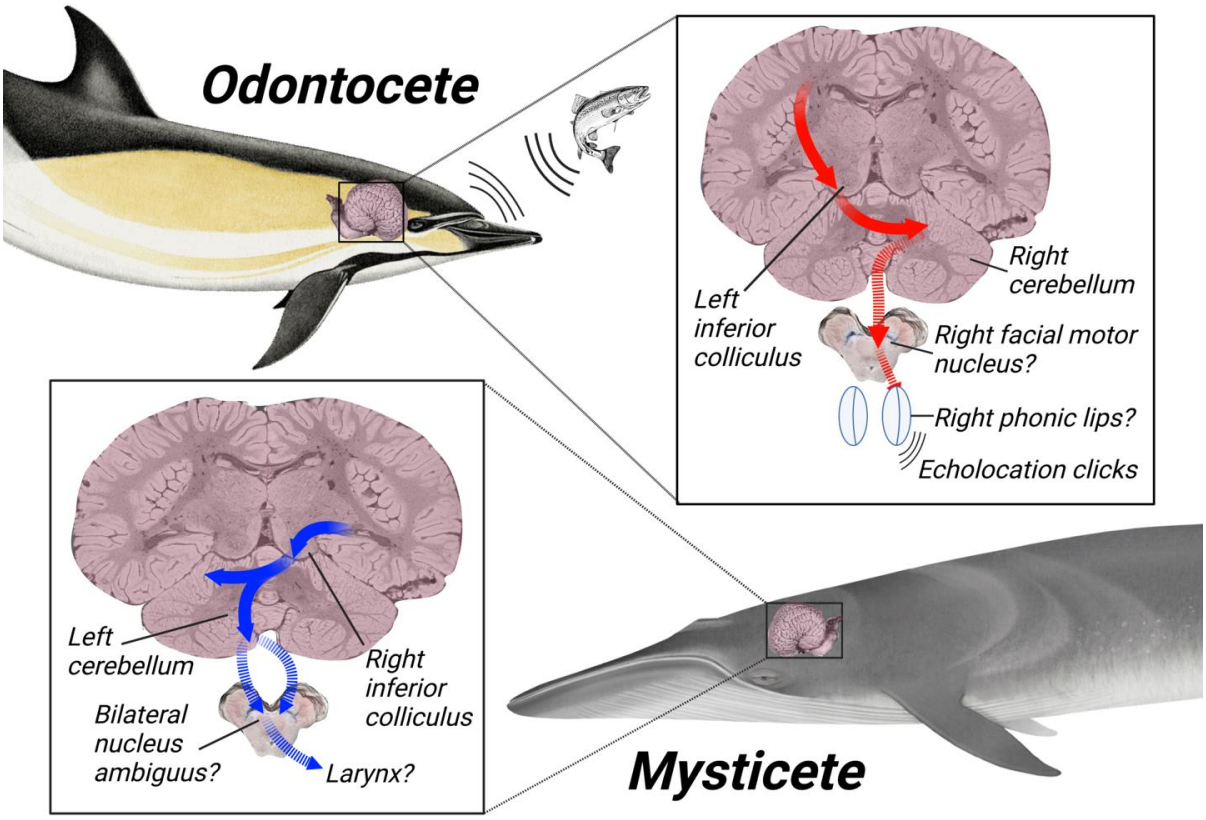
Topic: F.01. Neuroethology

Support: Human Frontiers Science Program Grant "Social Origins of Rhythm"

Title: Echolocating and non-echolocating whales have conserved ascending auditory pathways but differentially lateralized auditory-cerebellar connections

Authors: *S. FLEM, P. COOK;
Div. of Social Sci., New Col. of Florida, Sarasota, FL

Abstract: We report the first application of diffusion tractography to a mysticete, which was analyzed alongside three odontocete brains, allowing the first direct comparison of auditory pathways in echolocating and non-echolocating whales. Brains were imaged post-mortem at high resolution with a steady state free precession sequence optimized for dead tissue. We conducted probabilistic tractography to compare the qualitative features, tract strength, and lateralization of potential ascending and descending auditory paths in mysticetes and odontocetes. Tracts were seeded in the inferior colliculi (IC), a nexus for ascending auditory information, and the cerebellum, a center for sensorimotor integration. Direct IC to temporal lobe pathways were found in all animals, replicating previous cetacean tractography and suggesting conservation of the primary auditory projection path in the cetacean clade. Additionally, IC-cerebellum pathways were stronger in the odontocetes than the mysticete, suggesting a role as descending acousticomotor tracts supporting the rapid sensorimotor integration demands of echolocation. Further, in the mysticete, contralateral right IC to left cerebellum pathways were 17x stronger than left IC-right cerebellar tracts, while in odontocetes, the laterality was reversed, and left IC-right cerebellar tracts were 2-4x stronger than right IC-left cerebellar ones. The stronger left IC-right cerebellum connectivity in odontocetes corroborates the theory that odontocetes preferentially echolocate with their right phonic lips, as the right phonic lips are likely innervated by left-cortical motor efferents that integrate with left-cortical auditory afferents in right cerebellum. This interpretation is further supported by the reversed lateralization of IC-cerebellar tracts in the non-echolocating mysticete and by lateralized differences in the specific cerebellar targets of IC in each. This study establishes foundational knowledge on mysticete auditory connectivity and extends knowledge on the neural basis of echolocation in odontocetes.



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Poster

PSTR033: Sensory Motor Systems

Location: MCP Hall A

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Program #/Poster #: PSTR033.22/J5

Topic: F.01. Neuroethology

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Title: An evaluation of neuronal excitability, Ca homeostasis and inflammation on prepusle inhibition in mouse models

Authors: K. LIU[1], Z. WANG[2], J. YANG[4], R. S. ZHAN[1], C. A. DANZY[1], J. WANG[3], ***X. ZHAN**[1];
[1]Dept. of Physiol. and Biophysics, Howard Univ., Washington, DC; [2]Dept. of Anesthesiology, Pain and Perioperative Med., [3]Dept. of Human Anat., Zhengzhou Univ., Zhengzhou, China; [4]Dept. of Neurol., Guangzhou Med. Univ., Guangzhou, China

Abstract: The startle reflex, a robust, sensory-motor response that is an evolutionarily conserved defensive response across mammals. The prepulse inhibition (PPI) of startle reflex has been widely used as an assay in animals to model human diseases, such as schizophrenia, major depression and bipolar or autism spectrum disorders. Although the key circuit for startle reflex is well established, the results from different labs and animal models have shown a vast variation or contradiction. This is caused at least in part that the functionality of the circuit of reflex is also determined by its basic state such as neuronal excitability, Ca homeostasis, and inflammation. These factors are fundamental considerations to evaluate the usefulness of startle data in animal models. In this study, we attempted to evaluate auditory startle responses and the prepusle inhibition in C57/BL6, JPH3 and Cx3Cr1 KO mice. Mouse auditory startle responses were recorded by the Kinder Startle Monitor System. Harmaline, a putative agent (12.5 mg/kg, n = 22) on neuronal excitability reliably attenuated startle responses, but not the prepulse inhibition. In a TBI stroke model (n = 24), both the auditory startle and the PPI were decreased as well. However, loss of CX3CR1 (n = 13) to disrupt the signaling between neurons and microglia attenuated PPI but did not significantly affect TBI induced PPI reduction. In JPH3 KO mice (n = 42), in which the Junctophilin proteins that are required to maintain Ca homeostasis were deleted, both the startle responses and PPI were significantly reduced. These findings suggest sensory-motor integration is more sensitive to Ca homeostasis over neuronal excitability or inflammatory state. Caution should be exercised to interpret PPI data from different animal models with consideration of the effects on the key circuit of auditory startle reflex as well as neuronal excitability, Ca homeostasis and inflammatory state.

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Poster

PSTR034: Cellular Actions of Stress

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.01/J6

Topic: F.03. Stress and the Brain

Support: JSPS KAKENHI Grant Number 23K24775

Title: Expression of senescence-associated β-galactosidase in the hypothalamus of aged mice

Authors: *T. KOMORI[1], E. KURIYAMA[2], Y. MORIKAWA[1];
[1]Dept. of Anat. & Neurobio., [2]Dept. of Neurolog. Surgery, Wakayama Med. Univ., Wakayama, Japan

Abstract: Aging is an inevitable physiological process that involves a variety of cellular damage, leading to a gradual decline in physical and cognitive functions. The hypothalamus regulates many physiological processes essential for life, including feeding, reproduction, sleep, circadian rhythms, stress response, blood pressure, and core body temperature. Although decline of hypothalamic functions is one of the key factors to accelerate aging, the precise mechanisms are not fully understood. To gain further insights into the hypothalamic alterations with aging, we compared the expression of senescence associated-β-galactosidase (SA-β-gal), which increases in senescent cells as lysosomes begin to malfunction, in the hypothalamus between young (2 months old) and aged (12 months old) mice. In young mice, few expressions of SA-β-gal were observed in the hypothalamus. In aged mice, however, SA-β-gal was predominantly expressed in the cells surrounding the dorsal part of the third ventricles (subependymal region). Next, we characterized SA-β-gal-positive cells in this region. Immunofluorescence staining combined with SA-β-gal staining revealed that SA-β-gal-positive cells expressed glial fibrillary acidic protein (GFAP), but not expressed NeuN and Iba-1, markers of neuron and microglia, respectively. It has been reported that GFAP is expressed in neural stem cells (NSCs) in addition to mature astrocytes in the hypothalamus. To clarify whether SA-β-gal-positive cells are hypothalamic NSCs, we investigated whether SA-β-gal-positive cells express Sox2, a marker of NSCs, in the hypothalamus. Expression of Sox2 was observed in SA-β-gal-positive cells, indicating that SA-β-gal is expressed in subependymal GFAP-positive NSCs in the hypothalamus of aged mice. It has been reported that deletion of Sox2-positive cells (NSCs) in the hypothalamus led to accelerate aging in mice. In the hypothalamus, NSCs are localized in some regions, including hypothalamic parenchyma, subependymal region, and ependymal region (subpopulation of tanycytes). The present study showed that cellular senescence was initially induced in subependymal GFAP-positive NSCs during aging processes in the hypothalamus. These results suggest that dysfunctions of subependymal NSCs are one of the important trigger events to accelerate aging.

Disclosures: T. Komori: None. **E. Kuriyama:** None. **Y. Morikawa:** None.

Poster

PSTR034: Cellular Actions of Stress

Location: MCP Hall A

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Program #/Poster #: PSTR034.02/J7

Topic: F.03. Stress and the Brain

Support: NIMH R01 MH117459 to Elizabeth Gould

Title: Social and nonsocial environmental loss have differential effects on behavior and inhibitory synapses in the ventral hippocampus

Authors: *I. R. GORE, C. J. BROWN, R. C. WATERS, A. K. CARPENTER, E. GOULD; Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: In humans, psychological loss can be a precipitating event for the development of clinical depression and anxiety disorders. These losses can be mostly social, such as the death of a loved one or a relationship ending, or mostly nonsocial, like eviction or job loss. Both social and nonsocial losses have been linked to the development of anxiety disorders. Researchers have modeled combined social and nonsocial loss in rodents by transitioning them from social, enriched environments (EE) to individual, standard housing (Smith et al., 2017; Smail et al., 2023). This paradigm changes behaviors associated with avoidance, stress coping, and cognitive function, although it is not clear whether the effects are driven primarily by social or nonsocial loss. To address this question, we examined the effects of nonsocial loss by housing groups of male mice in EE for 4 weeks before moving them to standard cages, where they were pair-housed for 2 weeks . We then compared these results to those from mice that experienced complete social loss by transferring them from group housing to individual housing. Our findings indicate that mice in continuous EE exhibited decreased avoidance behavior and reduced social investigation time without deficits in social recognition compared to controls. Nonsocial loss restored avoidance behavior and social investigation to no difference from controls. However, compared to controls, social loss increased avoidance behavior and reduced novel social investigation, possibly indicating social avoidance. In rodents, avoidance and social recognition require neuronal oscillations in the ventral hippocampus (vHIP), which involve phasic firing of parvalbumin+ (PV+) inhibitory interneurons. Most PV+ cells are surrounded by perineuronal nets (PNN), extracellular matrix structures. PNNs concentrate GABAA synaptic receptors at the holes in their lattice-like structure, a function that may enable phasic firing (Wingert & Sorg, 2021). We found that EE living reduced expression of the GABAA receptor synaptic protein gephyrin in holes of PNNs in the vHIP, effects that may be linked to the behavioral changes we observed. We also observed decreased gephyrin expression in nonsocial loss mice, but this was accompanied by decreased extrasynaptic GABAAδ receptors, which play important roles in tonic inhibition. In nonsocial loss mice, decreased extrasynaptic GABAAδ receptors may compensate for decreased synaptic GABAA receptors after EE, thus restoring control-like behavior. Ongoing analyses will determine how these measures differ with social loss, as well as their contribution to vHIP behavioral function.

Disclosures: I.R. Gore: None. **C.J. Brown:** None. **R.C. Waters:** None. **A.K. Carpenter:** None. **E. Gould:** None.

Poster

PSTR034: Cellular Actions of Stress

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Program #/Poster #: PSTR034.03/J8

Topic: F.03. Stress and the Brain

Support: P20GM139753
R01DK047320
F32DK124963
NIDDK STEP-UP Program

Title: Glucocorticoid Regulation of Selenoprotein S in Hippocampal Cells

Authors: J. L. NICHOLSON, M. J. BERRY, *D. J. TORRES;
Pacific Biosci. Res. Ctr., Univ. of Hawai'i at Manoa, Honolulu, HI

Abstract: Glucocorticoid signaling in the brain can have pro-survival effects on memory and cognition, but long-term elevation can have negative consequences. Glucocorticoid over-activity can impair antioxidant enzymes, including the selenoprotein family, and heighten cellular vulnerability to oxidative damage. Higher glucocorticoid levels have also been associated with accelerated neurodegenerative pathology. Preliminary work with HT22 mouse hippocampal cells revealed that corticosterone application causes a decrease in Selenoprotein S, which may indicate an increased susceptibility to endoplasmic reticulum stress. We investigated this possibility further with experiments on HT22 cells to determine both the mechanisms through which corticosterone regulates Selenoprotein S, as well as the impact on the endoplasmic reticulum stress response. Additionally, we have detected changes in Selenoprotein S levels in the brains of mice administered corticosterone. Thus, HT22 cells may serve as a useful model for unraveling the mechanisms through which glucocorticoids may impair cellular health by altering selenoprotein levels.

Disclosures: J.L. Nicholson: None. **M.J. Berry:** None. **D.J. Torres:** None.

Poster

PSTR034: Cellular Actions of Stress

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Program #/Poster #: PSTR034.04/J9

Topic: F.03. Stress and the Brain

Support: Burroughs Wellcome Fund Grant 1064307
NIH Grant 5T32DA053558-03

Title: Stress-sensing microglia and habenular function

Authors: *A. CORONA[1], M. ISHIKAWA[1], V. MATHIS[2], L. WILLS[1], J. WANG[1], P. J. KENNY[3];
[1]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Cell. and Integrative Neurosci. Inst., Strasbourg, France; [3]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Dysregulated stress systems contribute to major depressive disorder, substance use disorders and other neuropsychiatric conditions that negatively impact human health. Persistent

stress can give rise to emotional and cognitive deficits. For example, individuals suffering from PTSD have marked deficits in their ability to process spatial information. Little is known about the mechanisms of stress-induced deficits in spatial encoding and related cognitive deficits. We confirmed that chronic stress precipitates spatial encoding deficits in mice during contextual fear conditioning. Stress increases the propensity of lateral habenula (LHb) neurons to emit high-frequency bursts of action potentials. This cellular adaptation contributes to stress-related behavioral abnormalities, including deficits in reward processing and cognition. Mechanisms by which stress increases the burst-firing of LHb neurons are poorly understood. Microglia play critical roles in maintaining homeostatic levels of neuronal activity. Our preliminary single-cell RNA sequencing and in situ hybridization data suggest that microglia but not neurons in the LHb express β2 adrenergic receptors (β2ARs). Using the recently published GRABNE sensor and fiber photometry we observed that stressors that increase burst-firing of LHb neurons enhanced norepinephrine (NE) signaling in the LHb of freely moving mice. Using current-clamp recordings to characterize the intrinsic activity patterns of LHb neurons, we found that lesioning microglia precipitated a stress-like increase in burst-firing of LHb neurons. We conducted fiber photometry experiments in mice expressing GCaMP6s in the LHb, with or without microglia depletion. Foot shocks evoked large-magnitude Ca2+ responses in control and microglia-deficient mice as expected. However, these responses persisted for a much longer period of time in the microglia-lesioned mice. Calcium activity in microglia was monitored on brain slices using a fluorescent microscope, and we showed that NE acted directly on LHb microglia via β2ARs to attenuate ATP-evoked calcium signaling in these cells, which is known to promote homeostatic interactions between microglia and activated neurons. These exciting preliminary data suggest that stress enhances NE signaling in the LHb, which acts via β2ARs to disrupt microglial surveillance of local neuronal activity, thereby promoting burst-firing of LHb neurons. In future experiments, we will investigate the role of β2AR-mediated NE signaling in microglia in regulating stress-induced cellular adaptations in the LHb and associated stress-induced deficits in spatial encoding.

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Poster

PSTR034: Cellular Actions of Stress

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.05/J10

Topic: F.03. Stress and the Brain

Support: R00 DA047426-01A1
PI's Start-Up Funds

Title: Identifying the role of microglia on matrix metalloproteinases activity during acute stress

Authors: *J. P. TABORDA-BEJARANO[1], M. L. ALLEN[1], M. MEYERINK[1], A. A. HOOSON[2], F. CHAURE[4], C. GARCIA-KELLER[3];
[2]Pharmacol. and Toxicology Dept., [3]Pharmacol. and Toxicology, [1]Med. Col. of Wisconsin, Milwaukee, WI; [4]Inst. of Biomed. Engin., Univ. of Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina

Abstract: The focus of our laboratory is to understand the underlying neurobiological consequences of stress that lead to substance abuse. Using a rodent model, we have shown that a single acute stress event (2-hour restraint), enhances drug use and induces enduring synaptic adaptations in the nucleus accumbens core (NAcore), resembling drug induced synaptic adaptations. Recent studies have shown the importance of microglia-neuron interaction in inducing synaptic adaptations by degradation of the extracellular matrix (ECM; proteinaceous network surrounding cells). Published work from the laboratory has shown that cocaine self-administration induces synaptic plasticity in NAcore (increased in spine density and glutamatergic currents), which is mediated through degradation of the ECM by matrix metalloproteinase 2 and 9 (MMP-2, -9, enzymes that catalytically cleavage the ECM). Therefore, since stress and drug use share common synaptic adaptations, here we ought to understand the role of microglia in this process by assessing the interplay between microglia and MMP activity. For this purpose, , we studied microglia morphology and MMP activity immediately after a 30-minute acute restraint stress or non-stress (sham) session. To inhibit microglia, we used a colony stimulation factor 1 receptor (CSF1R) inhibitor, PLX3397 (PLX), a receptor that has been shown to be essential for microglia survival and function. Rats received 2 injections of PLX intraperitoneally daily for 7 days prior to their stress or sham session. A dose response curve was performed using 1, 5 and 10 mg/kg doses of PLX and Vehicle. MMP-2,-9 enzymatic activity within the NAcore was measured by *in-vivo* zymography gel experiments. Immediately after the stress or sham session, animals were perfused the brain collected and sliced at 100 um and stained with Iba-1 (marker for microglia and macrophages) antibody. We used confocal microscopy to collect images for MMPs activity and microglia analysis. We utilized CellSelect 3Dmorph and ImageJ software to analyze microglia morphology and MMP activity respectively. Preliminary results have shown that all doses of PLX decreased MMP activity between PLX-stress and vehicle-stress animals. Changes in microglia morphology included reduced ramification index in vehicle-stress animals compared to vehicle-sham, and PLX-stress animals have increased ramification index. These results suggest that microglia may play a role in the stress induced NAcore synaptic adaptations by increasing the MMP-2,-9 activity. However, more experiments focusing on the enduring synaptic adaptations of the NAcore, and microglia are needed to evaluate the hypothesis.

Disclosures: J.P. Taborda-Bejarano: None. **M.L. Allen:** None. **M. Meyerink:** None. **A.A. Hooson:** None. **F. Chaure:** None. **C. Garcia-Keller:** None.

Poster

PSTR034: Cellular Actions of Stress

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.06/J11

Topic: F.03. Stress and the Brain

Support: CIHR Project Grant 178281

Title: The impact of chronic stress on the mouse cerebellum: from cells to behavior

Authors: *C. L. O'DONNELL[1,3,4], A. SUVRATHAN[2,3,4];
[1]Integrated Program in Neurosci., [2]Neurol. and Neurosurgery, Pediatrics, McGill Univ., Montreal, QC, Canada; [3]Ctr. for Res. in Neurosci., Montreal, QC, Canada; [4]BRaIN Program Res. Inst. of the McGill Univ. Hlth. Ctr., Montreal, QC, Canada

Abstract: The ability to respond and adapt to stressful environments is crucial for survival. The stress response, when mild and short in duration, is a normal part of everyday functioning. However, chronic exposure to stress causes widespread changes to neurophysiology and behavior that are often maladaptive. The cerebellum, a brain region known to be critical for sensorimotor functions, has also been found to regulate affective behaviors. Additionally, this region has been shown to undergo structural and functional alterations in response to stress in human and animal studies. Despite this, the impact of chronic stress on cerebellar cell physiology and cerebellum-associated behaviors has yet to be thoroughly characterized. To address this gap in understanding, we employed repeated restraint as a model to study the effects of chronic stress in male and female mice. Whole-cell recordings were used to investigate the electrophysiological properties of Purkinje cells, the sole output neurons from the cerebellar cortex, after chronic stress. Sensorimotor and affective behaviors, both known to be influenced by Purkinje cell activity, were assessed via the classic accelerating rotarod and open field tests. Strikingly, we observed a lobule-specific change to the input/output relationship of Purkinje cells in the cerebellar vermis after chronic stress. Furthermore, we found that the intrinsic excitability of Purkinje cells is impacted differently in lobule III, a region associated with sensorimotor functions, compared to lobule VI/VII, a region that has been implicated in affective behavior. The observed alterations in Purkinje cell properties were correlated with increased anxiety behavior but not deficits in rotarod motor learning. These results provide a critical first step towards understanding the full extent of cerebellar alterations induced by chronic stress and the behavioral consequences associated with them.

Disclosures: C.L. O'Donnell: None. **A. Suvrathan:** None.

Poster

PSTR034: Cellular Actions of Stress

Location: MCP Hall A

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Topic: F.03. Stress and the Brain

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NIH BX002604
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Title: Sex-dependent effects of chronic stress on HPA axis mitochondrial function

Authors: *A. CROCKETT[1], N. FRAMBES[1], E. CAVALLI[1], B. SRIVASTAVA[1], A. MULLALY[1], J. GARDINER[1], A. CHURILLO[1], L. FREEBURG[1], E. HARRINGTON[1], R. RODRIGUES DOS PASSOS[1], C. VIEIRA DOS SANTOS[1], S. WILCZYNSKI[1], F. PRIVIERO[1], R. WEBB[1], S. K. WOOD[3], F. SPINALE[4], M. RYAN[1], F. HOLLIS[2];
[2]Pharmacology, Physiology, and Neurosci., [1]Univ. of South Carolina, Columbia, SC;
[3]Pharmacology, Physiol. & Neurosci., [4]Univ. of South Carolina Sch. of Med., Columbia, SC

Abstract: Chronic stress exposure is increasing worldwide and is associated with the onset and severity of pathologies, including psychiatric diseases such as depression and anxiety. Women may be more susceptible to the effects of stress as they report higher levels of stress and psychiatric disorders compared to males. Women with stress-related disorders exhibit a significantly increased risk of comorbid cardiovascular disease (CVD); however, females are underrepresented in stress research and the biological pathways that account for sex differences in comorbid CVD are unclear. Mitochondria are dynamic organelles that adapt to fluctuating cellular energetic demands, which are increased under stress. Mitochondria also facilitate the synthesis and release of steroids, including glucocorticoids. This positions mitochondria as the first line of response to environmental challenges; however, the effects of chronic stress on mitochondrial function in hypothalamic pituitary adrenal (HPA) axis regions remain unclear, and data for sex differences are sparse. We hypothesized that chronic unpredictable stress (CUS) would induce sex-specific changes in mitochondrial function in stress sensitive regions. Adult male and female mice were exposed to 28 days of stress (CUS) or non-stress conditions (CON; light handling) to observe behavioral and physiological differences. We analyzed body weight gain, avoidance behavior in the elevated plus maze (EPM), systolic blood pressure (SBP), and assessed the estrous cycle. Mitochondrial respiration was analyzed via high-resolution respirometry. Stressed males exhibited a 37% reduction in body weight gain ($p=.011$; $n=17$) and a 33% decrease in % time spent in the open arms of the EPM ($p=.038$; $n=12$-16/group). We observed main effects of sex ($p=.004$) and stress ($p<.0001$) to increase SBP in males and females and a correlation approaching significance between SBP and avoidance behavior ($R2=.18$; $p=.052$ $n=4$-11/group). We observed a main effect of stress to decrease adrenal mitochondrial respiration ($p=.025$ complex I; $n=12$-18/group), amygdalar respiration of males ($p=.017$ complex I; $n=4$-7/group), and a significant interaction between stress and the estrous cycle in the hypothalamus ($p=.023$ complex I; $n=12$-17/group). Together, our findings support the hypothesis of a sex-dependent role of mitochondria in response to chronic unpredictable stress. Future

directions will investigate the functional role of mitochondria in sex-specific behavioral and cardiovascular changes to advance our understanding of stress-related disorders.

Disclosures: **A. Crockett:** None. **N. Frambes:** None. **E. Cavalli:** None. **B. Srivastava:** None. **A. Mullaly:** None. **J. Gardiner:** None. **A. Churillo:** None. **L. Freeburg:** None. **E. Harrington:** None. **R. Rodrigues dos Passos:** None. **C. Vieira dos Santos:** None. **S. Wilczynski:** None. **F. Priviero:** None. **R. Webb:** None. **S.K. Wood:** None. **F. Spinale:** None. **M. Ryan:** None. **F. Hollis:** None.

Poster

PSTR034: Cellular Actions of Stress

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.08/J13

Topic: F.03. Stress and the Brain

Support: AG082315

Title: Transcriptomic analysis of glucocorticoid treated neuronal cells implicates repetitive elements and its role in antidepressant response.

Authors: *J. GUO[1], S. SABUNCIYAN[2], R. LEE[3];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Pediatrics, Johns Hopkins Univ., Baltimore, MD; [3]Johns Hopkins Med., Baltimore, MD

Abstract: Chronic exposure to glucocorticoids (GCs) or stress can lead to a host of diseases such as cardiovascular disease, obesity, diabetes, and psychiatric disorders. The brain is particularly vulnerable as prolonged exposure to GCs is associated with depression. It is thought that GCs precipitate or exacerbate depressive symptoms by epigenetically altering the expression of genes that are important for neuronal function. To identify genes that are transcriptionally and epigenetically altered by GCs, we treated mouse neuronal cells with dexamethasone after which they were subjected to RNA-Seq, Methyl-Seq, and glucocorticoid receptor ChIP-Seq. Our analysis revealed that these treatments not only impact genes involved in inflammation and cell proliferation but also several classes of repetitive elements (REs), predominantly found on mouse Chromosome 11. Interestingly, neuronal expression of REs has been shown to correlate with exposure to early-life adversity. Further, the homologous intergenic region on human Chromosome 5 has been implicated in a genome-wide association study of MDD (depression) patient response to Selective Serotonin Reuptake Inhibitors (SSRI). We then asked whether GC-induced repeat expression may play a role in antidepressant response. Treatment of neuronal cells with the SSRI citalopram significantly attenuated GC-induced RE expression. Citalopram treatment also attenuated GC-induced loss of DNA methylation at the REs and other GC-regulated genes. Furthermore, introducing REs exogenously into neuronal cells significantly hampered their growth and proliferation. These findings suggest that the induction of RE

expression by GCs could contribute to depression by compromising cellular functionality and interfering with the efficacy of antidepressants.

Disclosures: **J. Guo:** None. **S. Sabunciyan:** None. **R. Lee:** None.

Poster

PSTR034: Cellular Actions of Stress

Location: MCP Hall A

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Program #/Poster #: PSTR034.09/J14

Topic: F.03. Stress and the Brain

Support: NIH Grant 5R01MH108342
NIH Grant 5T32GM008111

Title: Amygdala NPY-positive interneurons are activated and release NPY during stressful events

Authors: P. J. PEREZ[1], Y. LI[2], J. A. HARDAWAY III[1], *L. E. DOBRUNZ[3];
[1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]Peking Univ., Beijing, China; [3]Anat. and Neurobio., Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Anxiety disorders are the most common form of mental illness, and anxiety is a key symptom of post-traumatic stress disorder. However, knowledge about how traumatic events modulate neural circuits to induce anxiety is incomplete. It has long been known that the amygdala is a key area that processes stressful sensory information. Neuropeptide Y (NPY), a potent anxiolytic, has emerged as an important mediator of stress in the amygdala. In rodent models, NPY levels are reduced in the amygdala one week after exposure to a stressful event, suggesting chronic alteration of interneurons that produce NPY. Most studies focus on long-term changes induced by trauma, but very little is known about the acute response of NPY+ cells during a traumatic event. To date, no studies have measured in vivo NPY+ cell activity during a stressor, nor is it known if trauma causes sufficient activity to induce NPY release. Here we used footshock (1 mA, 1 s, x10, 5 min interval) as a physical and psychological stressor. To investigate amygdala NPY+ cell activation, we injected a virus for a cre-dependent genetically encoded calcium indicator, GCaMP, into amygdala of male and female NPYcre mice and recorded NPY cell activity in vivo using fiber photometry. NPY+ interneurons in amygdala were robustly activated by footshock, as seen by an increase in GCamP fluorescence. This was observed in both male and female mice, with no sex-dependent differences. Next, we wanted to determine if NPY is released during a traumatic event via a GRAB sensor. GRAB-NPY is a novel genetically encoded sensor that increases its fluorescence upon NPY binding, however, it had not been validated in vivo. We first expressed pan-neuronal GRAB-NPY in amygdala together with cre-dependent ChrimsonR, a red-shifted optogenetic activator. Photostimulation of NPY+ cells produced a frequency-dependent increase in the GRAB-NPY fluorescent intensity that was blocked by the Y1 receptor antagonist BIBO 3304. Together these results confirm the

sensor's ability to detect endogenous NPY release. We next tested for NPY release during footshock and observed an increase in the fluorescent signal of GRAB-NPY during this aversive stimulus. This is the first measurement of NPY release in vivo during a salient stimulus and indicates that trauma causes sufficient activation of NPY cells to trigger NPY release. Taken together, these results reveal a role for NPY+ interneurons during aversive events and potential involvement in shaping amygdalar microcircuitry during acquisition of traumatic memories.

Disclosures: P.J. Perez: None. **Y. Li:** None. **J.A. Hardaway:** None. **L.E. Dobrunz:** None.

Poster

PSTR034: Cellular Actions of Stress

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.10/J15

Topic: F.03. Stress and the Brain

Title: Microrna profiles of neuronal-enriched exosomes in depression.

Authors: *H. KRONMAN[1,2], S. AZAM[5,2], B. BIGIO[3], C. NASCA[4];
[1]NYU Sch. of Med., Brooklyn, NY; [3]Psychiatry, [4]Psychiatry, Neurosci. & Physiol., [2]NYU Sch. of Med., New York, NY; [5]Nathan Kline Inst., Orangeburg, NY

Abstract: Prior studies showed increased levels of neuronal exosomes in patients with major depressive disorders (MDD), that they contain altered cargo of molecular markers of the insulin signaling cascade as compared to age- and sex-matched healthy control subjects. Here, we used our state-of-the-art technology to isolate neuronal exosomes from subjects with MDD and unbiased microRNAseq to identify and characterize those specific microRNAs involved in the regulation of the insulin signaling cascade and the related pathway of mitochondrial metabolism. We used available plasma samples from our prior studies of depression for a total of ~30 samples. Bioinformatic analyses showed that we can consistently detect microRNAs in neuronal exosomes as shown by a robust count of high quality reads with Phred score > 30 and a length of 21-23 nt, which is the characteristic length of microRNAs. Advanced bioinformatic analysis of the microRNA data are ongoing to map differentially expressed microRNA profiles in the relation to clinical symptoms. Parallel studies in rodents are aimed at mechanistically validating the role of the identified pathways in brain plasticity. We hope that the current work will aid further development of mechanistic models of personalized medicine.

Disclosures: H. Kronman: None. **S. azam:** None. **B. Bigio:** None. **C. Nasca:** None.

Poster

PSTR034: Cellular Actions of Stress

Location: MCP Hall A

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Program #/Poster #: PSTR034.11/J16

Topic: F.03. Stress and the Brain

Support: R00 DA047426-01A1
PI Startup Funds

Title: Rat NAcore D1- and D2-MSN cell specific activity in response to a stress associated cue

Authors: *M. L. ALLEN[1], F. CHAURE[2], M. MEYERINK[1], J. P. TABORDA-BEJARANO[1], C. GARCIA-KELLER[1];
[1]Med. Col. of Wisconsin, Milwaukee, WI; [2]Inst. of Biomed. Engin., Univ. of Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina

Abstract: Stress has been identified as an environmental risk factor for substance use disorder (SUD). Clinical studies have shown that 40-60% of patients with post-traumatic stress disorder (PTSD) also develop SUD. Patients with a comorbidity of PTSD and SUD show greater drug use and worse treatment outcomes than patients with either disorder alone. The nucleus accumbens core (NAcore) contains 90% GABAergic medium spiny neurons (MSNs) that express D1- or D2- dopaminergic receptors. NAcore is a part of the reward and motivation circuitry, and its neurons are susceptible to synaptic adaptations due to stress and addiction. In relation to motivated behaviors, traditionally, D1-MSNs promote reward seeking and D2-MSNs promote aversive behaviors. However, more recent studies have shown that both cell types can promote reward-seeking behaviors. Therefore, here we want to understand how these MSNs respond to a stress associated cue and relate to active and passive coping behaviors using a defensive burying (DB) task. Eight-week-old, transgenic D1- and D2-cre rats were virally injected with GCaMP virus and a GrIN lens was implanted in the NAcore. After 3 weeks, rats were stressed (restraint stress) or non-stress (sham) for 90 minutes and paired with an odor, that became the stress conditioned stimulus (stress CS). Twenty-one days after this event, animals were then placed in an open field box to complete a 15- minute defensive burying task for 3 consecutive days (day 21, 22, and 23) to evaluate initial exposure to the CS and extinction to the CS. During this task, the bedding and CS were placed at opposing ends of the box. Active coping was characterized by increased burying while passive coping was characterized by increased immobilization/freezing response. We also performed a within subject longitudinal analysis of calcium dynamics of D1- and D2-MSN in freely moving animals while performing a task using a miniature microscope (Inscopix, Inc.). There were differences in the cell specific Ca2+ transient activity for stressed animals. These differences were seen when comparing DB1 vs DB3 where we saw an increase in D2-MSN in the mean event rate of the cells that coincided with a decrease in active coping suggesting that D2-MSNs encode extinguishing to the CS. We think that these experiments can provide some insight into how mechanisms of stress responses to a stress CS can correlate to patterns of Ca2+ single cell specific activity that may underlie susceptibility to SUD. In the future, we consider that these experiments may help us to understand the role these cells play in triggering drug seeking in response to a CS.

Disclosures: M.L. Allen: None. **F. Chaure:** None. **M. Meyerink:** None. **J.P. Taborda-Bejarano:** None. **C. Garcia-Keller:** None.

Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.01/J17

Topic: F.03. Stress and the Brain

Support: NIMH Biobehavioral Research Awards for Innovative New Scientists (BRAINS) (R01MH129643)
The Starr Foundation

Title: Uncovering the impact of early life stress on genomic organization across development with single cell resolution

Authors: *R. LIN[1], K. SULLIVAN[2], C. J. PENA[1];
[1]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Life Sci. Inst., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Early life stress (ELS) primes individuals to be more sensitive to future stressors, increasing the likelihood of adult depression or anxiety disorders. Despite this, the biological basis of this stress sensitivity attributed to ELS is not well understood. Both clinical and preclinical investigations show that ELS disrupts VTA development and function, including altered dopamine neuron excitability, reward processing, and response to stressors. Previous research has identified transcriptional and epigenetic alterations in adult VTA following ELS, and that epigenetic state crystalizes in the late postnatal period which coincides with a stress sensitive period, but how stress might interact with molecular development is still unknown. Furthermore, the VTA has a diverse population of different cell types, and previous research has lacked cellular specificity. To determine how ELS impinges on epigenetic development, we utilized 10X Genomics Chromium Multiome ATAC + Gene Expression assays to achieve single cell resolution across a postnatal time course from standard-reared (P1-2, 7, 14, 21 and >60; n=20) and ELA-exposed (P14, 21, and >60; n=12) male and female mice. ~360,000 individual nuclei were successfully sequenced to a depth of ~40,000 paired end reads for each of the ATAC and RNA libraries per sample, with an average of 10,000 nuclei per individual sample. We identified ~90,000 unique Tn5 accessible peaks per nuclei corresponding to ~3% of genome represented by peak enrichment. Additionally, ~26,000 transcripts per sample or ~2000 transcripts per nuclei were identified. Nuclei cluster into expected cell types based on published adult midbrain atlases. Interestingly, across cell types, ELS largely opens chromatin in VTA, although the extent and timing of this pattern varies by cell type. Current analysis is constructing trajectories of normative chromatin opening and closing in order to determine whether ELS opens genomic regions ne novo or prevents their normal closing. The resulting developmental atlas will elucidate the chromatin accessibility of VTA cell types under typical developmental conditions, and by comparison, it will reveal how ELS alters these trajectories.

Disclosures: R. Lin: None. **K. Sullivan:** None. **C.J. Pena:** None.

Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.02/J18

Topic: F.03. Stress and the Brain

Support: NIH R00MH115096 (CJP
NIH R01MH129643 (CJP)
PNI Research Innovator Award (CJP)
NYSCF (CJP)

Title: Effects of pharmacological manipulation of thyroid hormone signaling during development

Authors: *S. BENNETT[1], J. Y. CHEUNG[2], C. J. PENA[3];
[1]Princeton Univ., Princeton, NJ; [3]Princeton Neurosci. Inst., [2]Princeton Neurosci. Inst., Princeton, NJ

Abstract: Numerous factors, such as stress, have been implicated to affect thyroid function. We have previously demonstrated that exposure to stress during a sensitive period of development (postnatal day P10-P17) elevated plasma thyroid stimulating hormone levels in juvenile males and females, indicating suppressed thyroid hormone signaling. In adulthood, animals that underwent early life stress (ELS) showed behavioral abnormalities, but the subgroup of animals that received a short duration of levothyroxine (LT4, synthetic thyroid hormone), following ELS (P21-P25) through their drinking water showed improved behavior. Furthermore, qPCR findings showed administration of LT4 to rescue select genes directly affected by ELS in the ventral tegmental area (VTA). This suggested that pharmacological treatment is sufficient to restore the detrimental impact ELS has on thyroid signaling in the VTA. However our findings also highlighted a gap in understanding the action of this drug in rescuing deleterious effects of ELS thus necessitating a genome wide approach to help identify potential molecular mechanisms and pathways that underlie this treatment response.
In order to determine whether thyroid supplementation rescues gene expression across the genome, and whether thyroid inhibition mimics ELS across the genome, we generated 4 groups of mice, utilizing both sexes: standard-reared, ELS, ELS with 5 days of LT4, and standard-reared with methimazole (an antithyroid agent, from P10-P25 in their drinking water). Brains were taken at P25, and RNA was extracted from VTA for RNA-seq. Ongoing analysis is comparing both differentially expressed genes within each comparison, as well as the ability of LT4 to rescue or methimazole to mimic ELS across the genome using a rank-rank hypergeometric computational analysis approach. In parallel, treated siblings were allowed to age to adulthood, subject to adult social defeat stress, and tested on a battery of behavioral tests.
Using a multi-method approach will allow us to analyze how manipulating thyroid function affects the maturation of the brain and further provide insight into the relationship between thyroid, stress, and subsequent behavioral and gene expression changes.

Disclosures: S. Bennett: None. **J.Y. Cheung:** None. **C.J. Pena:** None.

Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.03/J19

Topic: F.03. Stress and the Brain

Title: Maternal separation stress affects the gut microbiota-brain axis in neonatal mice via metabolomic changes in breast milk

Authors: *E. A. MADY[1,2], H. M. EL-HUSSEINY[3], J. KAMBE[1], S. MIYATA[1], T. TERRAJIMA[1], R. INOUE[4], Y. YAMAMOTO[1], K. NAGAOKA[1];
[1]Cooperative Div. of Vet. Sci., Tokyo Univ. of Agr. and Technol., Tokyo, Fuchu, Japan; [2]Benha University, Benha, Egypt; [3]Dept. of Surgery, Anesthesiol., and Radiology, Fac. of Vet. Med., Benha Univ., Benha, Egypt; [4]Dept. of Applied Biol. Sci., Setsunan Univ., Osaka, Japan

Abstract: Mice studies have shown that stress caused by the separation of mother and neonates during infancy adversely affects the brain development of the neonate. Breast milk is an important factor in the acquisition and formation of gut microbiota. Thus, we hypothesized that changes in milk composition due to maternal stress would affect the formation of the gut microbiota, resulting in adverse effects on brain development. Neonatal mice were separated from their mothers for 3 hours daily from postnatal day (PND) 3 to 20. Milk components were profiled by metabolomic analysis, and milk corticosterone level was also measured; neonates were euthanized, and collected samples were used to evaluate the cecal microbiome, serum and cecal metabolome, and gene expression in the prefrontal cortex. Milk metabolome profiles differed between the control and maternal separation (MS) groups: myristic acid and ethanolamine were significantly elevated in the milk metabolome of MS mothers, as was milk corticosterone. The cecal microbiome of the pups showed significant changes between the two groups: levels of *Akkermansia muciniphila* (*A. muciniphila*) in the MS group were significantly lower than those in the control group ($p = 0.038$). Inosine and threonic acid were decreased in the cecal metabolome, while inosine and hypoxanthine were decreased in the serum metabolome. In contrast, myristic acid was significantly increased in the cecal and serum metabolome of the MS group. Tryptophan Hydroxylase 2 (*Tph2*) and 5-hydroxytryptamine receptor 1B (*Htr1b*) expression were significantly decreased in MS neonate versus control neonate ($p = 0.011$ and 0.013 for *Tph2* and *Htr1b*, respectively). These findings suggest that the decline of inosine is correlated to the decrease of serotonergic gene expression with a potential incidence of depression and are in line with (Gonçalves FM et al., 2017), who detailed the anti-depressant activity of inosine in mice. We further examined the effect of oral supplementation of myristic acid (1000 mg/Kg BW, PND 3 to PND 14) on the abundance of *A. muciniphila*. Myristic acid-treated neonates had significantly reduced *A. muciniphila* compared to vehicle-treated animals. It was reported that *A. muciniphila* could produce inosine (Tang L et al., 2024), thus we propose the decrease of cecal and serum inosine due to the low abundance of *A. muciniphila* in MS neonate. In conclusion, the transfer of high levels of myristic acid to neonates via MS breast milk

in the early postnatal period may disrupt the blood inosine-mediated serotonin signaling pathway by reducing *A. muciniphila* levels during gut microbiota formation.

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Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

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Topic: F.03. Stress and the Brain

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Office of Naval Research (ONR) N00014-19-1-2149
The Pritzker Neuropsychiatric Disorders Research Consortium
Grinnell College Center for Careers, Life, and Service

Title: A meta-analysis of the effects of early life stress on the prefrontal cortex transcriptome suggests long-term effects on myelin

Authors: T. DUAN[1], *M. H. HAGENAUER[2], D. NGUYEN[1], A. BADER[1], E. I. FLANDREAU[3], P. M. MARAS[2], R. M. S. DE LIMA[4], M. J. MEANEY[5], S. J. WATSON, Jr.[6], H. AKIL[2];
[1]Grinnell Col., Grinnell, IA; [2]Univ. of Michigan, Ann Arbor, MI; [3]Psychology Dept., GVSU, Allendale, MI; [4]McGill Univ., Montreal, Montreal, QC, Canada; [5]Douglas Hosp Res. Ctr., Verdun, QC, Canada; [6]MNI, Michigan Neurosci. Inst., Ann Arbor, MI

Abstract: Early life stress (ELS) refers to exposure to negative childhood experiences, such as neglect, disaster, physical, mental, or emotional abuse. ELS can permanently alter an individual's brain, leading to cognitive impairment, sensitivity to future stressors, and mental health risks. The prefrontal cortex (PFC) is a key brain region implicated in the effects of ELS. To better understand the effects of ELS on the PFC, we ran a meta-analysis of publicly available transcriptional profiling datasets. We identified four datasets (GSE89692, GSE116416, GSE14720, GSE153043) that characterized the long-term effects of multi-day ELS paradigms (maternal separation for >3hrs/day or limited nesting) in male and female laboratory rodents (rats, mice) during the postnatal period (between postnatal days 2-20). The outcome variable was gene expression in the PFC later in life (late juveniles or adults) as measured by microarray or RNA-Seq.
To conduct the meta-analysis, we extracted log2 transformed gene expression data and sample metadata from the Gemma database of curated and re-analyzed gene expression studies. After subsetting to the relevant samples (PFC, no intervention beyond ELS) and removing outliers, the final sample size was n=60 (GSE116416 n=23 (no outliers); GSE116416 n=21 (2 outliers);

GSE14720 n=7 (no outliers); GSE153043 n=9 (1 outlier)). We excluded data from genes (defined by Entrez ID) that lacked variability in expression. We calculated ELS vs. Control differential expression using the limma pipeline (for microarray datasets) or the limma-trend pipeline (for RNA-Seq datasets), followed by an empirical Bayes correction. Meta-analysis was conducted by fitting a random effects model to the ELS vs. Control effect sizes (Log2 Fold Changes or Log2FC) and their respective sampling variances from each study.
We reached stable meta-analysis estimates for 12,152 genes. Two results survived false discovery rate correction (FDR<0.05): 1) the down-regulation of Claudin 11 (*Cldn11*: Log2FC=-0.31, FDR=0.00047), a myelin component and regulator of oligodendrocyte proliferation and migration, and 2) the upregulation of Solute Carrier Family 30 Member 3 (*Slc30a3*: Log2FC=0.18, FDR=0.0047), a zinc transporter found in synaptic vesicles. Amongst the top twenty results, there was also a downregulation of other myelin-related genes (Myelin Associated Glycoprotein (*Mag*): Log2FC=-0.25, FDR=0.093; Mal, T Cell Differentiation Protein (*Mal*) - a.k.a. Myelin And Lymphocyte Protein: Log2FC=-0.29, FDR=0.109). These findings suggest that ELS during critical periods of development may produce long-term effects on the efficiency of transmission in the PFC.

Disclosures: **T. Duan:** None. **M.H. Hagenauer:** None. **D. Nguyen:** None. **A. Bader:** None. **E.I. Flandreau:** None. **P.M. Maras:** None. **R.M.S. de Lima:** None. **M.J. Meaney:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.05/J21

Topic: F.03. Stress and the Brain

Support: Vera and John Schwartz Family Professorial Chair in Neurobiology at the Weizmann Institute of Science
Ruhman Family Laboratory for Research on the Neurobiology of Stress
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The Adelis Foundation
Sonia T. Marschak

Title: Prenatal stress induces long term behavioral effect while altering the development of CGE- and MGE-derived GABAergic neurons in the mPFC

Authors: *K. SHOSHANI-HAYE, G. FRIEDLANDER, S. ALMEIDA-CORREA, A. CHEN; Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Individual differences in stress responsivity throughout life, in humans and other animals, are tremendously affected by early life stress. The disparity between individuals starts

as early as in-utero, during the critical period of brain development. Robust evidence show that prenatal stress (PNS) plays a significant role in increasing one's likelihood to suffer from numerous psychiatric conditions, including major depressive disorder, schizophrenia, and stress-related disorders. However, the biological mechanism underlying the predisposing effect of PNS is still unknown.
We utilize a mouse model to mimic the adverse effect of PNS shown in humans. Psychogenic stress is induced during gestation (E1.5-E16.5), and behavioral outcome is measure in adult male and female offspring (P56 ICR mice, n=10 per group). We use RNA-sequencing to identify novel pathways effected by PNS, focusing on the medial prefrontal cortex (mPFC), due to its strong involvement in emotional processing and its dysregulation in psychiatric disorders. We follow up with Immunohistochemistry assay using antibodies for Lhx6 and Nr2f2 to mark MGE- and CGE-derived inhibitory neurons as well as 5-Ethynyl-2′-deoxyuridine (EdU) to track newborn cells (injected at either E11.5, E14.5 or E16.5, n=10).
Our results show that mice exposed to prenatal stress were characterized by higher anxiety-like behavior. Interestingly, this effect was more profound in males than in females. Using RNA sequencing we characterize molecular differences between prenatally stressed mice and control on postnatal day 1 (P1). Our RNA-seq results suggest that PNS may affect integral brain development through regulation of genes related to neuronal cell migration, specifically those involved in inhibitory neuronal migration. Correspondingly, histological analyses provide compelling evidence of altered ratios of inhibitory neuron subpopulations at P1 in the mPFC. Our data demonstrates an increase in CGE-derived inhibitory neurons and concurrent decrease in MGE-derived neurons.
Our findings emphasize an intricate interplay between PNS and cortical inhibitory neurons development. They not only expand our understanding of stress-induced alterations in inhibitory neuron subpopulation, but also highlight specificity of these effects within a key brain region implicated in emotional regulation and cognitive processes. alterations in inhibitory neuron subpopulations during early development can have profound long-lasting implications for synaptic connectivity and neural circuit function, potentially predisposing individuals to psychiatric disorders later in life.

Disclosures: **K. Shoshani-Haye:** None. **G. Friedlander:** None. **S. Almeida-Correa:** None. **A. Chen:** None.

Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

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Program #/Poster #: PSTR035.06/J22

Topic: F.03. Stress and the Brain

Support: Cornell University New Frontier Grant A88-3129
NIH NRSA Grant F32HD105396

Title: Impacts of paternal deprivation and social stress on patterns of neural activation in the social brain

Authors: *L. SAILER[1], L. A. O'CONNELL[2], A. G. OPHIR[1];
[1]Psychology, Cornell Univ., Ithaca, NY; [2]Biol., Stanford Univ., Stanford, CA

Abstract: Parental neglect, physical trauma, and other forms of early-life adversity (ELA) produce individual variation in developing resiliency or susceptibility to stress. This highlights the importance of understanding how some individuals minimize health-compromised outcomes, whereas others succumb to stress and develop mood disorders. Oxytocin and vasopressin modulate activity in the social decision-making network (SDMN) to permit the expression of social behaviors and stress responses. The impact of ELA on signaling molecules could therefore explain natural variability in developmental outcomes. Caregiving by fathers impacts offspring social and neural development in species that show paternal care. Prairie voles reared in the absence of fathers exhibit social behavior impairments and develop altered patterns of region-specific oxytocin and vasopressin expression. Chronic social defeat stress (CSDS) is an established paradigm that models ELA and can trigger enduring alterations in behavioral and neural development. We designed a two-hit model of stress to assess the distinct and combinatorial influence of paternal deprivation and CSDS on the sociability of developing prairie voles. We identified activated SDMN brain regions using immunohistochemical detection of phosphorylated ribosomal protein S6 (pS6) within oxytocinergic and vasopressinergic neurons. The lateral septum (LS), a central node of the SDMN, was significantly more active in socially defeated vs stress-naïve subjects. Next, we used phosphoTRAP to molecularly profile LS-activated neurons and we report many genes that may influence stress resilient and susceptible phenotypes. Our two-hit model of stress demonstrates how experience-based and mechanistic sources of resilience interact, and reveals risk factors associated with stress susceptibility.

Disclosures: L. Sailer: None. **L.A. O'Connell:** None. **A.G. Ophir:** None.

Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

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Program #/Poster #: PSTR035.07/J23

Topic: F.03. Stress and the Brain

Support: NIMH MH108286
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NICHD HD105771

Title: Neurodevelopmental changes produced by paternal stress are associated with increased sperm respiration and motility in mice and men

Authors: *A. JENG[1], N. R. MOON[2], C. BRAGA[3], N. A. LEU[4], C. N. EPPERSON[2], T. L. BALE[5];
[1]Psychiatry, Univ. of Colorado Anschutz Med. Campus, Denver, CO; [2]Psychiatry, Univ. of Colorado Anschutz Med. Campus, Aurora, CO; [3]Federal Univ. of ABC, Sao Bernador do Campo, Brazil; [4]Biomed. Sci., Univ. of Pennsylvania, Philadelphia, PA; [5]Psychiatry, Univ. of Colorado Anschutz Med. Sch., Aurora, CO

Abstract: Chronic stress increases lifetime disease risk, influencing mental wellness and offspring neurodevelopmental outcomes. Following chronic stress, mice sire offspring with reduced stress axis responsivity. As sperm are highly protected and transcriptionally inert, environmental signals, such as chronic stress, likely impact somatic epididymal cells rather than the sperm directly. Prior mechanistic studies in mice demonstrated that epididymal epithelial cells (EECs) transmit essential maturation signals, such as extracellular vesicles (EVs), to sperm. Further, we revealed that prior stress alters small non-coding RNA (sncRNA) content in mouse sperm and EEC-derived EVs. Given these findings and the potential role of sncRNA to act as causal agents in the germline transmission of paternal experience, we tested for relationships between sncRNA expression and perceived stress scores (PSS) in a longitudinal repeated sampling human cohort. We identified several microRNA (miRNA) that were normally lowly expressed in men but dynamically responsive to prior perceived stress. We also examined the hypothesis that EVs influence sperm mitochondrial respiration and motility by incubating EVs secreted from stress-treated EECs with sperm and found significant increases in sperm mitochondrial respiration and motility. Similarly, in our longitudinal human cohort study, we assessed the association between sperm motility and PSS and found that increased PSS 3 months prior to sample collection was again significantly associated with increased sperm motility. Together, these findings demonstrated that stress alters somatic EECs and the cargo of secreted EVs, subsequently influencing sperm sncRNA composition and physiology. We are currently examining how increased sperm motility and sncRNA content remodeling influence reproductive outcomes and offspring neurodevelopment. Specific studies focused on the function of identified miRNA from our human sperm results are comparing embryo developmental and implantation rates in mice. We hypothesize that changes in concentrations of stress-responsive miRNA function to increase developmental rates at the expense of precise brain maturation. Determining how these EV and sperm changes following stress are conveyed at conception and alter fetal brain development is essential to identify environmental risk and resilience factors.

Disclosures: A. Jeng: None. **N.R. Moon:** None. **C. Braga:** None. **N.A. Leu:** None. **C.N. Epperson:** None. **T.L. Bale:** None.

Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.08/J24

Topic: F.03. Stress and the Brain

Support: CIHR
FRQS
HBHL

Title: Oligodendrocyte-lineage cells and myelin in the human basolateral amygdala: a study of childhood maltreatment, depression, and age

Authors: *K. PERLMAN[1], E. CURTO[3], S. BARNETT BURNS[2], M.-A. DAVOLI[4], N. MECHAWAR[5];
[1]McGill Univ. Integrated Program in Neurosci., Verdun, QC, Canada; [2]McGill Univ. Integrated Program in Neurosci., Montreal, QC, Canada; [3]Douglas Mental Hlth. Univ. Inst., Montreal, QC, Canada; [4]Douglas Mental Hlth. Inst., Verdun, QC, Canada; [5]Douglas Inst., Montreal, QC, Canada

Abstract: Introduction: Childhood maltreatment increases the risk of psychiatric illness, including depression and suicide. Consistently, fMRI studies have shown that the basolateral amygdala (BLA) displays altered activity to affective stimuli in individuals who experienced child abuse (CA). Mouse models have causally implicated early life stress with myelin changes in the BLA. This study aimed to characterise the relationships between the following metrics and CA, depression, and age in post-mortem human BLA tissue: 1) mature oligodendrocyte (OL) and oligodendrocyte precursor cell (OPC) gene expression, 2) myelin coverage area of axons, and 3) OPC and OL cell densities. Methods: Frozen left hemisphere BLA was obtained from the Douglas-Bell Canada Brain Bank, with donor information characterized using validated psychological autopsy methods to form the following matched groups: depressed suicides with a history of CA, depressed suicides without a history of CA, and psychiatrically healthy controls. A novel fluorescence-assisted nuclear sorting (FANS) method using combinations of SOX10 and CRYAB immunofluorescence was used to isolate OPCs and OLs, the extracted RNA from which was then input into a custom nanoString panel. Colocalization of immunofluorescence of NF-H and MBP, to label axons and myelin respectively, was used to calculate area fraction coverage. Finally, RNA fluorescent *in situ* hybridization was used to probe OL (MYRF+) and OPC (PDGFRa+) densities. Results: The nanoString panel results revealed divergent patterns between OPCs and OL gene expression with respect to CA, depression, and age. Pilot results indicate that an average of 32.6% of BLA axons are myelinated in humans, with no significant effect of group on OPC density ($p = 0.32$) or OL density ($p = 0.54$). However, OPC density was found to be negatively correlated with age ($r = - 0.62$, $p = 0.0013$). We calculated the correlation between age and OPC densities or proportions in various previously published human datasets, replicating our findings in the vmPFC and dlPFC, which is notable given that this negative relationship is not observed in mice. Conclusion: Our preliminary results highlight the importance of post-mortem and cell type-specific human brain research, and further our understanding of the role of BLA OL-lineage cells and myelin in the neurobiological underpinnings of CA, depression, and aging.

Disclosures: K. Perlman: None. **E. Curto:** None. **S. Barnett Burns:** None. **N. Mechawar:** None.

Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

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Program #/Poster #: PSTR035.09/J25

Topic: F.03. Stress and the Brain

Support: 1R15HD110925-01A1

Title: Visualizing traumatic stress-induced structural plasticity in a medial amygdala pathway using mGRASP

Authors: *J. T. JACOBS[1], C. J. BARTSCH[2], N. MOJAHED[3], J. C. NORDMAN[4];
[1]Physiol., Southern Illinois Univ. Sch. of Med., Carbondale, IL; [2]Lab. of Neuropsychology, Natl. Inst. of Mental Hlth., Bethesda, MD; [4]Physiol., [3]Southern Illinois Univ., Carbondale, IL

Abstract: Traumatic stress has been shown to contribute to persistent behavioral changes, yet the underlying neural pathways are not fully explored. Structural plasticity, a form of long-lasting neural adaptability, offers a plausible mechanism. To scrutinize this, we used the mGRASP imaging technique to visualize synaptic modifications in a pathway formed between neurons of the posterior ventral segment of the medial amygdala and ventrolateral segment of the ventromedial hypothalamus (MeApv-VmHvl), areas we previously showed to be involved in stress-induced excessive aggression. We subjected mice (seven-eight weeks of age) to acute stress through foot shocks, a reliable and reproducible form of traumatic stress, and compared synaptic changes to control animals. Our data revealed an increase in synapse formation within the MeApv-VmHvl pathway post-stress as evidenced by an increase in mGRASP puncta and area. Chemogenetic inhibition of CaMKIIα-expressing neurons in the MeApv during the stressor led to reduced synapse formation, suggesting that the structural changes were driven by excitatory activity. To elucidate the molecular mechanisms, we administered the NMDAR antagonist MK-801, which effectively blocked the stress-induced synaptic changes. These findings suggest a strong link between traumatic stress and enduring structural changes in an MeApv-VmHvl neural pathway. Furthermore, our data point to NMDAR-dependent mechanisms as key contributors to these synaptic changes. This structural plasticity could offer insights into persistent behavioral consequences of traumatic stress, such as symptoms of PTSD and social deficits.

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Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

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Topic: F.03. Stress and the Brain

Support: George E. Hewitt Foundation for Medical Research Postdoctoral Fellowship
MH 096889

Title: The influence of early life adversity on PVT's response to reward, revealed by a double TRAP

Authors: *A. FLORIOU-SERVOU, R. WEBER, H. LIANG, C. KOOIKER, M. T. BIRNIE, M. GANTUZ, R. ROBERTS, A. MORTAZAVI, T. BARAM;
UC Irvine, Irvine, CA

Abstract: Background: Early-life adversity (ELA) is associated with cognitive and mental health problems later in life, and evidence in rodents points to a causal role of ELA, with structural and functional changes in the brain's reward circuitry. However, the mechanisms through which ELA changes the brain remain poorly understood. One emerging key node of the reward circuit is the paraventricular nucleus of the thalamus (PVT). The PVT is strongly and almost exclusively activated in the mouse brain early in life, it is re-activated during reward in adulthood, and inhibiting specific PVT domains alleviates ELA-induced reward deficits in a sex-specific manner. Therefore, the ELA experience could be encoded in the PVT and influence the PVT's response and function during reward behaviors later in life. Here, we explore how the PVT is itself affected by ELA at a molecular level. To this end, we explore the translatome of PVT cells activated early in life, and test the hypothesis that ELA causes enduring changes in their translational profiles, both at rest and in the context of reward. **Methods**: We crossed two strains of mice: a driver line expressing Fos-dependent CreERT2 that allows activity-dependent genetic labeling (TRAP2), with mice expressing a Cre-dependent ribosomal tag allowing translating ribosome affinity purification (TRAP). This approach isolated actively translated mRNA from cells that are activated during P6-P8, when mice are raised in either typical (control group) or ELA conditions. We collected the midline thalamus containing the whole PVT from 2-3 months old mice in baseline conditions, or one hour after the start of a reward paradigm. Subsequently we isolated the RNA bound to tagged ribosomes and performed next generation RNA sequencing. Mice from different groups were randomized during tissue collection and processing, and the experimenter was blinded throughout the experiment. **Results**: A. Strong enrichment in genes that are highly expressed in the PVT such as *Snca* and *Calb2*, and a reduction in genes that are less expressed in the PVT, confirmed that the isolated RNA was mainly from PVT cells. B. Relatively few genes were differentially expressed in adult ELA vs control mice during baseline conditions. C. In contrast, exposure to reward induced very different translatomic responses in ELA vs control mice, in a sex-dependent manner. **Conclusions**: Our results 1) indicate that ELA primes the PVT, influencing the way that the PVT responds to reward, and 2) highlight PVT's sexually dimorphic nature.

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Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

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Program #/Poster #: PSTR035.11/J27

Topic: F.03. Stress and the Brain

Title: Impact of early life adversity on microglial gene expression

Authors: *M. FANIKOS, C. R. CODY, H. C. BRENHOUSE;
Psychology, Northeastern Univ., Boston, MA

Abstract: The dynamic relationship between the nervous and immune systems plays an integral part in the long-term, sex-dependent impacts of adversity. Microglia, the primary neuroimmune cell, are long-lived cells and in early development can be programmed by environmental factors, which shape their behavior throughout the lifespan. For example, bacterial infection in the neonatal period leads to an exaggerated microglial response to immune stimulation with the bacterial toxin lipopolysaccharide (LPS) later in life. Microglia also respond to stress, and in adulthood acute and chronic stress can prime microglia to be more reactive to subsequent LPS challenge. The mechanism of adult stress-induced priming involves glucocorticoid receptor (GR) activation and disinhibition of microglia via downregulation of the CD200 receptor (CD200R). Importantly, early life adversity (ELA) leads to dysregulation of neuroimmune signaling and function. For example, ELA in the form of maternal separation (MS) increases microglial soma size in the prefrontal cortex (PFC) in juvenility, which is an indicator of immune activity. Moreover, following MS, adolescent males display heightened expression of the proinflammatory cytokine TNF-a in the PFC. However, it is unknown if ELA programs microglia via the same mechanisms as adult stress-induced priming, or if this priming is as long lasting as neonatal bacterial infection.
To address if ELA alters the developmental profile of priming related genes in microglia, rats underwent MS from postnatal day (P)2-P20. Microglia were isolated from the PFC on either P11 or P21 using magnetic activated cell sorting and qPCR was performed on the isolated microglia samples. Expression of genes involved in the microglial priming mechanism will be assessed, including GR, CD200R, and C/EBPB, a regulator of CD200R. We hypothesized that MS increases expression of C/EBPB, which in turn reduces expression of CD200R. Downregulation of CD200R is a necessary step in microglial priming, therefore these data provide evidence that MS primes microglia via a similar mechanism as in adulthood. Future experiments will investigate whether MS programs microglia to be more reactive to future LPS challenge, to inform the mechanisms that lead to the long-lasting consequences of ELA.

Disclosures: M. Fanikos: None. **C.R. Cody:** None. **H.C. Brenhouse:** None.

Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.12/J28

Topic: F.03. Stress and the Brain

Title: Prenatal stress modifies social behavior and the transcription of NMDA receptors.

Authors: *T. BUCK[1], E. DONG[2], M. MCCARTHY[1], A. GUIDOTTI[3], M. S. SODHI[1];
[1]Dept. of Mol. Pharmacol. and Neurosci., Stritch Sch. of Med., Loyola Univ., Maywood, IL; [2]Dept. of Psychiatry and Behavioral Hlth., Ohio State Univ., Columbus, OH; [3]Dept. of Psychiatry, Univ. of Illinois at Chicago, Chicago, IL

Abstract: Prenatal stress increases the risk of neurodevelopmental disorders, which commonly include social deficits. NMDA-type glutamate receptor (NMDAR) activity plays an important role in the cortico-hippocampal circuit. This circuit is abnormally regulated in neurodevelopmental disorders and mice exposed to prenatal stress. We have tested the hypothesis that prenatal restraint stress (PRS) in mice modifies the transcription of NMDAR subunits, leading to deficits in social behavior. We exposed pregnant mice to restraint stress three times daily for two weeks during gestation. At 10 weeks of age, male PRS offspring (n=20) and non-stressed controls (NS, n=20) were treated with haloperidol (1mg/kg), clozapine (5mg/kg) or saline twice daily for 5 days, before measuring social approach (SOC) in the three-chamber test, and locomotor activity. We used qPCR to measure transcription levels of NMDAR subunits GRIN1, GRIN2A, GRIN2B, and GRIN3A in the hippocampus and frontal cortex of the mouse subjects. PRS mice treated with either saline or haloperidol had reduced SOC relative to NS mice ($p \leq 0.004$). In contrast, clozapine-treated PRS mice had similar SOC compared to NS mice. Neither PRS nor medication reduced locomotor activity. These effects of PRS on SOC were associated with increased transcription of GRIN2A ($F_{1, 34}=4.30$, $p<0.05$), and GRIN2B genes ($F_{1, 34}=11.1$, $p=0.002$), in the hippocampus but not the frontal cortex. GRIN transcription in the frontal cortex correlated positively with SOC ($r^2=0.17$; $p=0.007$), but correlated negatively in the hippocampus ($r^2=0.76$; $p=0.00015$). The ratio of GRIN2A/ GRIN2B transcription is reported to increase during development but was lower in PRS mice ($F_{2,34}=6.5$, $p=0.004$). These results suggest that GRIN2A and GRIN2B transcript levels are modified in the hippocampus by PRS, leading to life-long social behavior deficits. The subunit composition of the NMDAR affects the receptor's affinity for glutamate, kinetics, pH sensitivity, and drug sensitivity. Altering the transcription levels of different NMDAR subunits would have a significant impact on the excitatory transmission in the corticolimbic circuit. Furthermore, these data have some overlap with the molecular pathophysiology of schizophrenia. As schizophrenia also has been associated with social withdrawal, increased GRIN2 expression in the hippocampus, and reduced GRIN2A/GRIN2B expression ratios in the hippocampus. These findings suggest that PRS in mice may have construct validity as a preclinical model for antipsychotic drug development.

Disclosures: T. Buck: None. **E. Dong:** None. **M. McCarthy:** None. **A. Guidotti:** None. **M.S. Sodhi:** None.

Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.13/J29

Topic: F.03. Stress and the Brain

Title: Early Stress Alters Hypothalamic Gene Expression related to Metabolism, Sex Hormones, Methylation, and Synaptic Organization in Adolescent Male Hamsters

Authors: *K. MORAN[1], T. M. MILEWSKI[2], J. P. CURLEY[3], Y. DELVILLE[4];
[1]Psychology, Univ. of Texas, Austin, Austin, TX; [2]Univ. of Texas at Austin, Austin, TX; [3]Psychology, Univ. of Texas At Austin, Austin, TX; [4]Psychology, Univ. of Texas at Austin Dept. of Psychology, Austin, TX

Abstract: In hamsters, a two-week exposure to chronic social stress in adolescence causes acceleration of agonistic behavior, enhanced adult aggression, impaired waiting impulsivity, and higher food intake, body fat, and long-term increased body weight. The present research examined changes in gene transcription in the hypothalamus caused by adolescent stress using RNA Tag-sequencing. We investigated the lateral, dorsomedial, and arcuate nucleus of the hypothalamus of 10 stressed and 10 control subjects. In each region, there were approximately 250 differentially upregulated and 250 downregulated genes. Many of the most significantly affected genes have been associated with metabolic and sex hormone function. For example, in the lateral hypothalamus, melanocortin 3 receptor, growth hormone releasing factor, both involved in metabolic processes, and neuropeptide VF precursor, involved in growth hormone inhibitory hormone production, were among the most upregulated in stressed subjects. In the dorsomedial hypothalamus, neuropeptide W, involved in feeding cessation, was significantly downregulated in stressed animals. Across both regions, G-protein coupled receptor 50, involved with sleep and sex-related mood disorders, was significantly altered, but in opposite directions. In the arcuate nucleus, a number of blood brain barrier- and inflammation-related genes were altered as well. Furthermore, there were consistent patterns of genetic ensembles identified through gene ontology analysis that were altered across all regions. Many of these involved roles in RNA processing, DNA methylation, and synaptic organization. These findings reinforce prior behavioral, hormonal, and metabolic changes observed in this developmental model, and help guide future directions of research related to the negative consequences of early life stress.

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Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

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Program #/Poster #: PSTR035.14/J30

Topic: F.03. Stress and the Brain

Title: Prenatal stress effects on sex differences in recognition memory and synaptic expression of AMPA-type glutamate receptors

Authors: *R. C. SOBREPENA, T. BUCK, M. MCCARTHY, M. S. SODHI;
Mol. Pharmacol. and Neurosci., Stritch Sch. of Med., Loyola Univ. Chicago, Maywood, IL

Abstract: Impaired AMPA-type glutamate receptor (AMPAR) function is associated with cognitive impairment. AMPARs are tetrameric membrane-bound proteins containing four GluA subunits (GluA1-4). The expression of AMPARs is linked to the density of dendritic spines, a cellular characteristic that is associated with cognitive function. Our overall hypothesis is that sex differences in cognition are due to variations in synaptic morphology and AMPAR expression in the hippocampus. We used the novel object recognition test (NORT) to assess recognition memory in mice. In this study, we used prenatal restraint stress (PRS) to model stress-induced cognitive impairment in mice. Pregnant Swiss Webster mice were exposed to restraint stress for 30 minutes, twice daily from gestation days 8 to 21. Preliminary results adult mouse offspring show that PRS reduced NORT performance in males ($p<0.1$) because male PRS (n=4) had reduced preference for the novel objects relative to non-stressed (NS) males, PRS females and NS females (n=11). Ongoing studies aim to test these findings in larger numbers of mice. To test if reduced cognitive behavior is related to synaptic function, we are using neuronal tracing (Imaris Filament Tracer software) to measure synaptic morphology in the CA1 of these mice (12-13 dendrites per mouse). Initial results show no sex differences in NS mice in total spine density or the density of mature spines. We are also performing immunohistochemistry (IHC) using an antibody against synaptophysin (SYN), which is a marker of axon terminals, and an antibody against extracellular AMPAR subunit GluA2. The degree of SYN and GluA2 co-localization is considered to be a marker of synaptic expression of GluA2. IHC was conducted in the stratum radiatum of the CA1 of the dorsal hippocampus (n=4, 5 z-stacks per subject). Initial results show that males had a higher density of axon terminals ($t_{18}=4.016$, $p<0.001$) and higher extracellular GluA2 expression ($t_{18}=3.490$, $p<0.01$) relative to females. Ongoing studies will test if sex differences of AMPAR-mediated pathways in the CA1 are associated with stress-induced impairments of cognitive behavior. This research aims to reveal novel targets for the development of therapies for cognitive dysfunction and the pathology of stress.

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Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

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Topic: F.03. Stress and the Brain

Support: NIH Grant 5R21MH119650
NIH Grant R01MH135390

Title: Maternal immune activation alters synaptic development and neuroimmune profiles in the amygdala in a nonhuman primate model

Authors: *K. HANSON[1], E. CARLSON[2], B. P. ANDER[3], S. KAMBOJ[4], K. D. MURRAY[5], J. A. VAN DE WATER[6], A. S. FOX[7], M. D. BAUMAN[8], C. M. SCHUMANN[9];
[1]UC Davis Med. Ctr., Sacramento, CA; [2]Psychiatry and Behavioral Sci., Univ. of California, Davis, Sacramento, CA; [3]Univ. of California Davis, Sacramento, CA; [4]Psychology, Univ. of California, Davis, Davis, CA; [5]Psychiatry & Behavioral Sci., Univ. California Davis, Davis, CA; [6]Rheumatology, Allergy, and Clin. Immunol., Univ. of California Davis, Sacramento, CA; [7]Psychology, Univ. of California - Davis, Davis, CA; [8]Univ. California, Davis, Sacramento, CA; [9]Dept. of Psychiatry, UC Davis Sch. of Med., MIND Inst., Sacramento, CA

Abstract: Maternal infection during pregnancy is associated with an increased risk of offspring neurodevelopmental disorders, including autism and schizophrenia. Evidence from preclinical models has highlighted key pathways by which exposure to maternal immune activation (MIA) in gestation may alter offspring neural development and behavior. The nonhuman primate (NHP) model of MIA provides a critical translational bridge for understanding the impact of MIA exposure on highly derived circuitry in the primate brain. Previous research in our Poly-IC-based rhesus macaque model has shown altered development of the prefrontal cortex in MIA-exposed NHPs, including reduced prefrontal cortical volumes, aberrant morphology of pyramidal neurons, and altered expression of synaptic genes. To examine changes in the amygdala and territories associated with socioemotional circuitry, we analyzed samples from the lateral and central nucleus of the amygdala in adolescent male macaques and controls using single nucleus RNA-seq (snRNA-seq). We identified unique cellular population profiles and region-specific patterns of differential gene expression. Specifically, genes associated with synaptic architecture and function were most strongly affected in MIA-exposed offspring. Preliminary evidence suggests altered distribution of synapses in MIA-exposed NHP offspring in amygdala lateral nucleus. Data from multiplexed assays for immune markers conducted in the same cohort across a broader distribution of anatomical regions in the temporal lobe further suggest altered expression of immune signalling molecules, including TGF-a, in the basolateral amygdala, as well as the entorhinal cortex and temporal white matter. These results support the hypothesis that prenatal MIA exposure results in lifelong changes in amygdala development that contribute to aberrant social behavior observed in the MIA-exposed NHP offspring.

Disclosures: K. Hanson: None. **E. Carlson:** None. **B.P. Ander:** None. **S. Kamboj:** None. **K.D. Murray:** None. **J.A. Van De Water:** None. **A.S. Fox:** None. **M.D. Bauman:** None. **C.M. Schumann:** None.

Poster

PSTR035: Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.16/J32

Topic: F.03. Stress and the Brain

Support: Division of Newborn Medicine's Academic Research Fund and the Boston Children's Health Physicians, Valhalla, NY

Title: Early life microbiome disbalance impact neuroendocrine outcomes in pre-pubertal mice in sexually dimorphic manner

Authors: *B. NANKOVA[1,2], F. HU[3], E. F. LA GAMMA[3];
[1]New York Med. Col., Brewster, NY; [2]Pediatrics, New York Medical College, Valhalla, NY; [3]Pediatrics, New York Med. Col., Valhalla, NY

Abstract: Recently, adverse exposures during a critical perinatal period of development have been recognized to result in undesirable gut microbial ecology (dysbiosis) in the offspring that negatively influences long term health. How gut dysbiosis affects neurobehavioral outcomes, the sympathoadrenal system and the newborn's ability to adapt to adverse conditions in the extrauterine environment is not well understood. In the current study C57Bl6 dams were given broad-spectrum antibiotics in the drinking water at parturition until weaning to perturb the normal seeding and maturation of the neonatal microbiome. Controls received sterile water. At weaning (before puberty) the offspring were subjected to behavioral tests or sacrificed after exposure to insulin-induced hypoglycemia. Fecal samples from each cohort were collected for whole genome shotgun taxonomic profiling and predictive functionality. Individual adrenal medulla samples were subjected to RNA sequencing transcriptome analysis to identify differentially expressed genes and molecular pathways between the cohorts contributing to the observed outcomes we previously characterized. Given that a gender bias has been detected in several neurodevelopmental disorders in humans we included "sex" as an important yet not frequently studied biological variable in the study. The offspring of control dams displayed sex-specific differences in microbiome composition, exploratory behavior, adrenal transcriptome profiles and basal urinary epinephrine levels. Maternal Abx during nursing caused: 1) microbial dysbiosis in the offspring evident by markedly enlarged ceca, no detectable by-products of bacterial fermentation, SCFA and dramatic changes in microbial composition, diversity (reduced - alpha Chao1, p &t 0.004 and p &t 0.005 resp.; and beta Bray-Curtis, p &t 0.003 diversity as compared to their respective controls) and metabolic activity; 2) altered the transcriptional landscape in the adrenals and attenuated peripheral stress responses; 3) increased anxiety-like measures, and decreased locomotor activity; all in a sexually dimorphic manner. We speculate that the observed gender differences in the weanling mice gut microbiome may contribute to sex-related disparities in neurodevelopmental disorders and ability for successful stress adaptations. These observations open paths for further studies that will provide a better understanding of their role in the interplay between microbial communities and the host during the critical period of postnatal brain development and help identify personalized nutritional and therapeutic strategies to promote long term health beginning from birth.

Disclosures: B. Nankova: None. **F. Hu:** None. **E.F. La Gamma:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.01/J33

Topic: F.06. Autonomic Regulation

Support: Branco Weiss Fellowship
Burroughs Wellcome Fund Career Award at the Scientific Interface
Warren Alpert Distinguished Scholar Award
Simons Collaboration in the Global Brain Training Grant
Life Sciences Research Foundation and Additional Ventures Fellowship
Harvard Mind Brain and Behavior Young Investigator Award

Title: Functional ontogeny of a sympathetic cardiac control system

Authors: *C. ADLER[1], L. HERNANDEZ-NUNEZ[2];
[1]Dartmouth Col., Hanover, NH; [2]Dept. of Mol. and Cell. Biol., Harvard Univ., Cambridge, MA

Abstract: The sympathetic nervous system plays a key role in fight-or-flight responses by adjusting the function of viscera to the metabolic requirements of vigorous behaviors. Studying the neural circuits that coordinate organ modulation in response to environmental changes has remained elusive given the limitations of mammalian models that require anesthesia and invasive procedures to access the sympathetic ganglia. Therefore, we leveraged the optical and genetic advantages of zebrafish, a model that has traditionally been used to study brain and behavior, to functionally study the sympathetic circuits for cardiac control in unanesthetized, intact, behaving animals. Using optogenetic activation of the superior cervical ganglia (SCG) at the anterior site of sympathetic neurons, we determined that the cardiac sympathetic system becomes functional at 7 days-post-fertilization (dpf) in larval zebrafish and increases its influence in cardiac regulation until 12 dpf. Calcium imaging in the SCG, revealed that there is a large diversity of temporal activity patterns, with more than ten groups of neurons with distinct dynamics. Our results establish the key stages for functional development of the cardiac sympathetic system and set the stage to expand the use of zebrafish in studying the neural circuits that control the heart.

Disclosures: C. Adler: None. **L. Hernandez-Nunez:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.02/J34

Topic: F.06. Autonomic Regulation

Support: Warren Alpert Distinguished Scholar Award
Burroughs Wellcome Fund Career Award at the Scientific Interface
Branco Weiss Fellowship
Simons Collaboration in the Global Brain Training Grant

Life Sciences Research Foundation and Additional Ventures Fellowship
Harvard Mind Brain and Behavior Young Investigator Award

Title: The development and function of sensory circuits for heart-brain interactions in larval zebrafish

Authors: *J. AVRAMI[1], L. HERNANDEZ-NUNEZ[2], A. KIM[3];
[1]MCB, Harvard Univ., Cambridge, MA; [2]Dept. of Mol. and Cell. Biol., Harvard Univ., Cambridge, MA; [3]Harvard Univ., Cambridge, MA

Abstract: Even though sensory feedback from the heart to the brain is essential for cardiovascular health, the developmental process of cardiac sensory innervation and the onset of interoceptive function remain understudied. Very few studies integrate the role of internal organs and the autonomic nervous system in the study of brain function. In order to study the emergence of viscerosensory feedback to the brain and its physiological role, we tracked the functional development of cardiosensory circuits in larval zebrafish. Using anatomical imaging, we discovered developmental landmarks for the formation of the vagal sensory ganglia that innervates the heart. We used aversive phototactic stimuli and calcium imaging to determine the onset of cardiac encoding properties of vagal sensory neurons; and laser ablations of the vagal sensory nerve to determine the onset of functional feedback to the brain. Our results establish the key stages for anatomical and functional development of the cardiac vagus nerve in zebrafish and set the stage for incorporating interoception into the study of brain internal states and natural behaviors.

Disclosures: J. Avrami: None. **L. Hernandez-Nunez:** None. **A. Kim:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.03/J35

Topic: F.06. Autonomic Regulation

Support: Branco Weiss Fellowship
Burroughs Wellcome Fund Carrer Award at the Scientific Interface
Warren Alpert Distinguished Scholar Award
Simons Collaboration in the Global Brain Training Grant
Life Sciences Research Foundation and Additional Ventures Fellowship
Harvard Mind Brain and Behavior Young Investigator Award

Title: Functional development of motor vagus circuits for cardiac control

Authors: *A. LAURENT RIOS, M. PHILLIPS, L. HERNANDEZ NUNEZ;
Harvard Univ., Cambridge, MA

Abstract: The study of naturalistic behaviors often focuses on external behaviors and brain activity, while ignoring other system components, such as internal organs and the autonomic nervous system. Autonomic circuits enable the brain to modulate visceral function, and viscera to modulate brain activity and behavior. To characterize system-level processing that incorporates the autonomic and central nervous systems, we need to conduct functional single-cell resolution imaging and perturbation of both systems. The only vertebrate model organism in which this process is feasible is the zebrafish larvae. In this study, we focused on the development of motor vagus circuits for cardiac control. Using anatomical imaging, we established developmental landmarks for motor vagus innervation of the heart. We then combined calcium imaging and optogenetics to determine the physiological role of the motor vagus neurons associated with the heart.

Disclosures: **A. Laurent Rios:** None. **M. Phillips:** None. **L. Hernandez Nunez:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.04/J36

Topic: F.06. Autonomic Regulation

Support: Branco Weiss Fellowship
Burroughs Wellcome Fund Career Award at Scientific Interface
Warren Alpert Distinguished Scholar Award
Simons Collaboration in the Global Brain Training Grant
Life Sciences Research Foundation and Additional Ventures Fellowship
Harvard Mind Brain and Behavior Young Investigator Award

Title: Molecular and functional profiling of vagal sensory neurons

Authors: *A. KIM, J. AVRAMI, L. HERNANDEZ NUNEZ;
Harvard Univ., Cambridge, MA

Abstract: Dysregulation of cardiac autonomic motor or sensory circuits can result in arrhythmias. Yet current surgical or pharmacological treatments primarily target motor circuits but not cardio-sensory neurons. Studying the role of cardio-sensory circuits in mammals has been challenging because in vivo neural activity measurements in vagal sensory neurons (the major conduits of viscerosensory information) require invasive procedures and anesthesia. Here, we leverage the larval zebrafish optical and genetic accessibility to track the function and development of vagal sensory neurons in 5 to 12 days post-fertilization fish. We have developed experimental protocols and techniques for molecular and functional profiling of the entire sensory vagus system in larval zebrafish throughout development. Our study sets the stage for systems-level studies of molecularly defined groups of vagal sensory neurons and their involvement in cardiac arrhythmia, as well as modulation of brain activity and behavior.

Disclosures: **A. Kim:** None. **J. Avrami:** None. **L. Hernandez Nunez:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.05/J37

Topic: F.06. Autonomic Regulation

Support: JST ERATO (JPMJER1801)
The Institute for AI and Beyond of the University of Tokyo

Title: Volitional control of heart rate

Authors: ***A. YOSHIMOTO**[1], S. MORIKAWA[2], E. KATO[1], H. TAKEUCHI[2], Y. IKEGAYA[1]; [1]The Univ. of Tokyo, Tokyo, Japan; [2]Grad. Sch. of Sci., The Univ. of Tokyo, Tokyo, Japan

Abstract: Heart rate (HR) is primarily regulated by the autonomic nervous system, but it can also be voluntarily regulated when individuals receive real-time feedback about their HR. However, the neural mechanism that underlies the biofeedback has not been fully elucidated. Herein, as a pioneer of animals' biofeedback experiments, we established a rat model of HR biofeedback in which the neocortex and the medial forebrain bundle were stimulated as the HR feedback and reward, respectively. Rats learned to reduce their HR within 30 min, achieving an approximately 50% reduction after 5 days of 3-h feedback training, a feat unattainable with HR feedback or reward stimulation alone or with their random time stimulation. The reduced HR persisted for at least 10 days after the 5-day training period, while the rats exhibited anxiolytic behavior and an elevation in blood erythrocyte count. We sought brain regions that are activated during feedback, using immunohistochemistry for c-Fos as a marker for neuronal activity. Brain areas that exhibited significant increases in c-Fos-positive cells involved the anterior cingulate cortex (ACC) and the anterior insular cortex (AIC). Muscimol inactivation of the ACC, but not the AIC, impaired biofeedback-induced bradycardia. Moreover, inactivation of ACC neurons projecting to the ventromedial thalamic nucleus (VMT) prevented the biofeedback-induced bradycardia. VMT-projecting ACC neurons exhibited theta-band field oscillations during operant training, and optogenetic theta-rhythm stimulation of the ACC-to-VMT pathway replicated the bradycardia. VMT neurons receiving synaptic inputs from the ACC send synaptic projection to the dorsomedial hypothalamus (DMH), and DMH neurons send projection to the nucleus ambiguus (Amb), the autonomic nervous center innervating postganglionic parasympathetic neurons in the heart. Our findings highlight the ACC→VMT→DMH→Amb→heart projection as a top-down pathway for volitional HR regulation. We also found that both VMT-projecting and MDT-projecting ACC neurons were activated during training and involved in the top-down control of HR. We speculate that the ACC and MDT form a reciprocal circuit that may function as a generator of theta oscillations and that the activity of this circuit is in turn transmitted from the ACC to the VMT and subsequently relayed to the DMH, Amb, and heart.

Disclosures: **A. Yoshimoto:** None. **S. Morikawa:** None. **E. Kato:** None. **H. Takeuchi:** None. **Y. Ikegaya:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.06/K1

Topic: F.06. Autonomic Regulation

Support: NIH R01 HL141198
HL164571

Title: Deletion of TRPV1 alters the expression and activities of P2X3 receptors in muscle dorsal root ganglion neurons of experimental peripheral artery disease

Authors: Q. LI[1], ***J. LI**[2];
[1]Penn State Col. of Med., Hershey, PA; [2]Penn State Coll Med., Hershey, PA

Abstract: In peripheral artery disease (PAD), the metaboreceptor and mechanoreceptor in muscle afferent nerves contribute to accentuated sympathetic nerve activity and arterial blood pressure via a neural reflex (termed exercise pressor reflex). Particularly, muscle metabolites such as adenosine triphosphate and products of oxidative stress etc. in active muscles respectively stimulate purinergic P2X3 receptors (P2X3) and transient receptor potential cation channel V1 (TRPV1) in muscle afferent nerves, inducing the reflex sympathetic and blood pressure responses. Previous studies also indicated that P2X3 and TRPV1 have an interaction in regulating the neural functions of sensory nerves. The purpose of this study was to determine the effects of removal of TRPV1 on the expression and activities P2X3 receptors in muscle dorsal root ganglion (DRG) neurons. An experimental PAD was induced by 72-hour femoral artery occlusion (FAO). Western blotting analysis was used to examine the expression of P2X3 in DRG tissues. The whole cell patch clamp was used to examine currents evoked by activation of P2X using α, β-methylene ATP. Resiniferatoxin (RTX, intraperitoneal injection) was previously given to abolish TRPV1 in DRGs. In results, RTX significantly decreased the protein levels of P2X3 receptors in DRGs and attenuated the density of transient P2X currents in muscle DRG neurons of FAO group and respective control. However, RTX amplified the density of sustained P2X currents in muscle DRG neurons and the effect was less in FAO group. In conclusion, TRPV1 can alter the expression and activities of P2X3 in muscle afferent nerves. The regulatory effects of TRPV1 on the transient and sustained P2X currents appear to be different which is likely a part of mechanisms involved in autonomic responses of PAD.

Disclosures: **Q. Li:** None. **J. Li:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.07/K2

Topic: F.06. Autonomic Regulation

Support: NIH Grant NHLBI R01 HL141560

Title: Heart Failure depresses vagal afferent transmission at the nucleus of solitary tract (NTS) in rats.

Authors: *L. G. FERNANDES[1], A. RADOVIC[2], E. BEAUMONT[1];
[1]Biomed. Sci., East Tennessee State Univ., Johnson City, TN; [2]East Tennessee State Univ., Johnson City, TN

Abstract: Vagus nerve stimulation (VNS) therapy is a current treatment for heart failure with reduced ejection fraction (HFrEF). Typically, VNS is administered at a frequency of 5 Hz with an intensity that induces slight bradycardia during stimulation. This study explores the impact of VNS on the integration of vagal afferents on Nucleus Tractus Solitarius (NTS) neurons in control and HF rats (ejection fraction < 60%) using various VNS protocols. Sprague-Dawley rats with pressure overload underwent a thoracic aortic constriction twelve weeks before terminal electrophysiology experiments and were compared to healthy controls. For terminal patch clamp experiments, the brainstem was removed under isoflurane anesthesia to obtain a horizontal brainstem slice containing the solitary tract (ST) and medial NTS. The brain slice was maintained in physiological cerebrospinal fluid (CSF) for whole-cell voltage-clamp recordings. Electrical shocks to the ST produced fixed latency evoked excitatory postsynaptic currents (eEPSCs) with a jitter < 200usec, identifying NTS neurons with monosynaptic afferent input. EPSCs with jitter > 200usec were considered polysynaptic. To mimic clinical VNS, ST stimulation protocols of 14 sec were used, including: 1) continuous 1 Hz stimulation, 2) continuous 5 Hz stimulation, 3) continuous 20 Hz stimulation and 4) burst stimulation with 4 pulses delivered at 300 Hz with an interburst interval (IBI) of 1 sec. Results showed no difference in the frequency and amplitude of spontaneous EPSCs from second-order neurons in HF rats compared to controls. Alternatively, the short 50 Hz stimulation protocol revealed that HF rats had reduced amplitude of eEPSCs ($p = 0.016$), attenuated frequency-dependent depression ($p = 0.035$) and higher failure rates ($p = 0.02$) compared to controls. Additionally, NTS neurons in HF rats exhibited a lower frequency ($p = 0.045$) and amplitude ($p = 0.03$) of asynchronous EPSCs compared to control. Variance-mean analysis revealed reduced quantal size ($p = 0.03$) and fewer release ($p = 0.006$) sites in HF rats compared to controls. VNS stimulations for 14 sec at 1Hz, 5Hz, 20Hz and burst 300 Hz elicited a decrease in evoked EPSC amplitude and higher failure rates in NTS second-order neurons in HF rats compared to controls ($p < 0.05$). Interestingly, the burst 300 Hz using 4 pulses protocol did not induce failures in both HF and control neurons. In conclusion, vagal afferent terminals exhibited marked synaptic depression compared to controls. Given that VNS therapy improves cardiac function, its effect may be linked to the restoration of synaptic properties for the central integration of vagal afferents at the NTS level.

Disclosures: L.G. Fernandes: None. **A. Radovic:** None. **E. Beaumont:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.08/K3

Topic: H.03. Decision Making

Support: Neurological Foundation of New Zealand 2325 PRG
Wellcome Trust UK WT 110157/Z/15/Z

Title: Variable cardiac responses after manipulations to non-human primate or rodent mediodorsal thalamus

Authors: B. A. L. PERRY[1], J. MENDEZ[2], E. PREMEREUR[3], V. PELEKANOS[4], J. C. DALRYMPLE-ALFORD[5,6], J. HAMILTON[5], ***A. S. MITCHELL**[5];
[1]Univ. of Oxford, Oxford, United Kingdom; [2]Biomed. Sci., Univ. of Exeter, Exeter, United Kingdom; [3]KU Leuven, Leuven, Belgium; [4]Univ. of Nottingham, Nottingham, United Kingdom; [5]Univ. of Canterbury, Christchurch, New Zealand; [6]New Zealand Brain Research Institute, Christchurch, New Zealand

Abstract: Cardiac changes are linked to mental health issues and neurodegeneration, with them contributing a role to cognition and emotion. Some of the brain structures involved in cognitive and emotional processes also comprise a central automatic network responsible for the modulation of cardiovascular output. The mediodorsal thalamus (MD) is involved in higher cognitive processes and is also known to be connected to some key neural structures of the central automatic network. However, it is unclear whether the MD has any role in regulating cardiovascular function. Here, we show in non-human primates that discrete manipulations to the MD using either microstimulation during anaesthetized functional neuroimaging or localized excitotoxic infusions, led to observable and variable changes in the heart rate of female and male rhesus macaque monkeys. Additionally, heart rate and respiration rate showed variable changes in male rats that received localized excitotoxic MD infusions under general anaesthesia, while for sham lesion rats these physiological measures were unaffected. Our findings suggest the MD has a role in autonomic cardiac regulation. Consequently, this role may interact with the MD's identified role in higher cognitive functions, and provide an important physiological link for cognition in frontal cortico-thalamocortical circuits.

Disclosures: B.A.L. Perry: None. **J. Mendez:** None. **E. Premereur:** None. **V. Pelekanos:** None. **J.C. Dalrymple-Alford:** None. **J. Hamilton:** None. **A.S. Mitchell:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.09/K4

Topic: F.06. Autonomic Regulation

Support: NIH Grant HL098602
NIH grant HL128454
NIH grant HL166183

Title: Impact of Corticotropin-releasing hormone (CRH) on the synaptic transmission of GABAergic and non-GABAergic neurons of the nucleus tractus solitarii (nTS)

Authors: *P. BARCELLOS-FILHO[1,2], H. DANTZLER[2], D. D. KLINE[2];
[1]Univ. of Missouri, Columbia, MO; [2]Biomed. Sciences/Dalton CRC, Univ. of Missouri, Columbia, Columbia, MO

Abstract: The nTS works as the primary center for integrating sensory afferents, playing a critical role in maintaining cardiorespiratory homeostasis across a variety of stressors. In addition, the paraventricular nucleus of the hypothalamus (PVN) significantly contributes to the regulation of cardiorespiratory function, in part, through its nTS projections that contain CRH. Within the nTS, we have shown that this neuropeptide increases nTS activity and influences the cardiorespiratory response to hypoxia. However, its specific impact on the phenotype of neurons within the nTS remains unclear. We hypothesized the excitatory influence of CRH is prevalent on non-GABAergic neurons of nTS, with distinguished function of this neuropeptide subject to the phenotype of these neurons[DK1]. Male and female transgenic GAD1-EGFP mice [strain FVB-Tg (GadGFP) 45704Swn/J, Jackson Laboratory, 4-5 weeks] were used to distinguish GABAergic and non-GABAergic neurons. Horizontal brainstem slices were generated, and using whole-cell patch-clamp recordings, we examined synaptic neurotransmission and electrophysiological properties of monosynaptic nTS neurons of GABAergic and non-GABAergic nTS neurons. Excitatory postsynaptic currents (EPSCs) and were examined during aCSF control, CRH (300 nM, 5 min) and wash. In the presence of CRH, network-driven spontaneous (s)EPSCs amplitude decreased in GABAergic neurons and not in non-GABAergic neurons. sEPSC frequency was not altered by CRH in either group. The amplitude of afferent-evoked (TS-)EPSC decreased in GABAergic neurons yet increased in non-GABAergic neurons in the presence of CRH. CRH promoted cellular depolarization primarily in non-GABAergic neurons. The expression of CRH receptors (via RNAscope) within nTS showed a prevalent expression of CRHR2 compared to CRHR1, indicating this response is mediated by CRHR2. Altogether, our data shows that CRH individually influences nTS activity, which is dependent of the neuron phenotype.

Disclosures: P. Barcellos-Filho: None. **H. Dantzler:** None. **D.D. Kline:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.10/K5

Topic: F.06. Autonomic Regulation

Support: NIH grant HL154512

Title: Diminished Calcineurin Activity in the Hypothalamus Augments Sympathetic Outflow by Potentiating α2δ-1-bound NMDA Receptor Activity in Spontaneously Hypertensive Rats

Authors: *J.-J. ZHOU[1], J.-Y. SHAO[2], S.-R. CHEN[2], Z.-Y. YE[2], H.-L. PAN[2];
[2]Anesthesiol. and Perioperative Med., [1]The Univ. of Texas MD Anderson Cancer Ctr., Houston, TX

Abstract: Calcineurin is a Ca^{2+}/calmodulin-dependent protein phosphatase, and calcineurin inhibitors cause hypertension by augmenting sympathetic outflow and glutamate NMDA receptor (NMDAR) activity in the hypothalamic paraventricular nucleus (PVN). Increased NMDAR activity in the PVN also plays a key role in elevated sympathetic vasomotor tone in spontaneously hypertensive rats (SHR), a commonly used animal model of primary hypertension. In this study, we determined whether calcineurin signaling in the PVN is altered in SHR. Calcineurin phosphatase activity in the PVN was much lower in SHR than in normotensive Wistar Kyoto rats (WKY). Systemic treatment with tacrolimus, a specific calcineurin inhibitor, caused a persistent increase in arterial blood pressure (ABP) in WKY but did not affect ABP already elevated in SHR. Co-immunoprecipitation revealed that tacrolimus treatment markedly increased α2δ-1-GluN1 protein complex levels in PVN synaptosomes in WKY, but not in SHR. Brain slice recordings showed that tacrolimus treatment significantly increased presynaptic and postsynaptic NMDAR activity in spinally projecting PVN neurons in WKY, but not in SHR. Furthermore, microinjection of tacrolimus into the PVN significantly increased renal sympathetic nerve activity and ABP in WKY; these effects were blocked by an NMDAR antagonist. In contrast, microinjection of tacrolimus into the PVN had no significant effect on renal sympathetic nerve activity or ABP in SHR. Additionally, systemically administered memantine or gabapentin substantially reduced higher ABP in SHR and in tacrolimus-treated WKY. These findings suggest that constitutive calcineurin activity in the PVN is diminished in SHR, which contributes to elevated sympathetic outflow by potentiating α2δ-1-bound NMDAR activity of PVN presympathetic neurons.

Disclosures: **J. Zhou:** None. **J. Shao:** None. **S. Chen:** None. **Z. Ye:** None. **H. Pan:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.11/K6

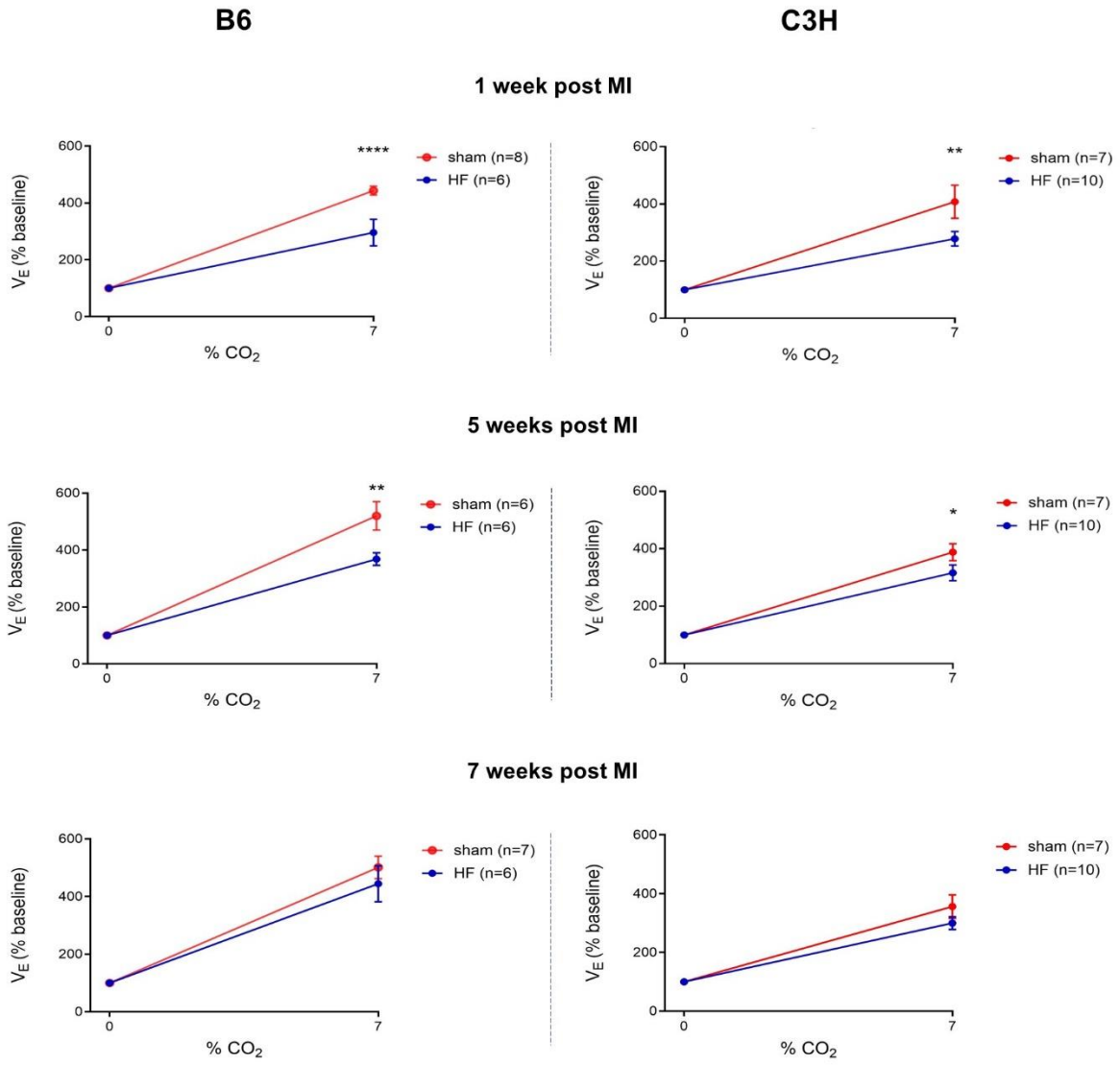
Topic: F.06. Autonomic Regulation

Support: NIH/NINDS – R01 NS123155
NIH/NINDS – R01 NS113764
NIH/NINDS – R25 NS079173

Title: Dynamic changes over time in central chemosensitivity following ischemic heart failure: a comparative analysis of two different mouse strains

Authors: *C. BORRELLI[1], G. B. RICHERSON[2];
[1]The Univ. Of Iowa Neurosci. Grad. Program, Iowa City, IA; [2]Dept Neurol, Univ. of Iowa, Iowa City, IA

Abstract: *Background**:*** Increased ventilatory response to hypercapnia (HCVR) is a major pathophysiological trigger of central apneas and ventilatory instability in HF, potentially representing an interesting therapeutic target. However, few studies evaluated the central component of HCVR in rodent models of HF. Moreover, the temporal evolution of central HCVR alteration has never been addressed. *Aim:* Evaluating central HCVR and ventilatory instability and its evolution in time in a mouse model of ischemic HF. *Methods:* HF was induced by permanent ligation of the left descending coronary artery (myocardial infarction: MI) in adult male B6 (HF n=16, sham n=8) and C3H (HF n=11, sham n=7) mice. HF was confirmed via echocardiography 1 week post-surgery. Central HCVR (5 minutes 7% CO_2 stimulus in 50% O_2) and 12-hours breathing (7:00 am - 7:00 pm) were addressed at 1, 5 and 7 weeks post HF induction. Central HCVR was expressed as percentage of change of minute ventilation from baseline, and apneas were defined as breathing cessation for more than 1 second. *Results:* B6 mice showed a significant reduction of central HCVR at 1 and 5 weeks, but not at 7 weeks post-surgery (Figure). Interestingly, B6-HF mice showed a significant reduction in the number of apneas at 1 week compared to shams (median [interquartile range] sham: 14 [10-17] vs. HF: 4 [1-6] events/hour, p=0.01), but not at 5 and 7 weeks post-surgery. C3H mice also showed a reduction of central HCVR at 1 and 5 weeks post-surgery, but not at 7 weeks (Figure). However, the number of apneas/hour was only different 5 weeks post HF induction (sham: 10 [8-13] vs. HF: 20 [13-26] events/hour, p=0.01). *Conclusions:* Central HCVR is reduced acutely in mouse models of ischemic HF, and it recovers over time. Distinctive mouse strains show different ventilatory profiles, indicating that attention to the strain should be paid when designing experiments. Furthermore, central HCVR shows a time-sensitive alteration after HF induction, suggesting that therapeutic strategies might have different effects if initiated at different times after HF.



Disclosures: **C. Borrelli:** None. **G.B. Richerson:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.12/K7

Topic: F.06. Autonomic Regulation

Support: Helen Dorris Foundation
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Scripps Research
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Title: Genetically defined vagal sensory neurons mediate the Bezold-Jarisch reflex and induce syncope

Authors: *J. MA[1], J. W. LOVELACE[4], S. YADAV[1], S. UGOCHUKWU[1], K. CHHABRIA[2], H. SHEN[5], Z. PANG[7], T. QI[8], Y. ZHANG[9], T. VAISSIÈRE[11], S. TAN[6], G. RUMBAUGH[11], L. YE[10], D. KLEINFELD[3], C. STRINGER[12], V. M. AUGUSTINE[1];
[2]Physics, [1]UCSD, San Diego, CA; [3]UCSD, La Jolla, CA; [4]Neurobio., UC San Diego, La Jolla, CA; [6]Neurosci., [5]The Scripps Res. Inst., San Diego, CA; [7]Dorris Neurosci. Ctr., The Scripps Res. Inst. The Scripps Res. Inst. - Grad. Program, La Jolla, CA; [9]Neurosci., [8]Scripps Res. Inst., La Jolla, CA; [10]Scripps Res. Inst., san diego, CA; [11]Univ. of Florida–Scripps Biomed. Res., Jupiter, FL; [12]HHMI Janelia Res. Campus, Ashburn, VA

Abstract: Genetically defined vagal sensory neurons mediate the Bezold-Jarisch reflex and induce syncope Detecting and integrating visceral sensory information is essential for survival and well-being. Disturbing this process may lead to physiological and mental diseases. The heart is a crucial organ modulating both physiology and higher order brain functions such as cognition and emotion. It continuously sends sensory information to the brain through complicated neural systems (i.e., vagus nerve) and alters brain states via activating cardiac reflexes. For example, the Bezold-Jarisch reflex (BJR), first described in 1867, is a cardioinhibitory reflex speculated to be mediated by vagal sensory neurons (VSNs) that also triggers syncope (fainting). However, the molecular identity, anatomical organization, physiological characteristics and behavioral influence of cardiac VSNs remain mostly unknown because of the closed loop nature of the cardiovascular system. Here, we found that VSNs that express neuropeptide Y receptor Y2 (NPY2R) predominately connect the heart ventricular wall to the area postrema (AP). Optogenetic activation of NPY2R VSNs elicits the classic triad of BJR responses- hypotension, bradycardia and suppressed respiration and further causes an animal to spontaneously faint. A panoply of phenotypes reflected in clinical syncope response profiles were also observed with photostimulation, including reduced cardiac output, cerebral hypoperfusion, pupil dilation, and eye-roll. Additionally, large scale Neuropixels brain recordings showed that this manipulation causes suppression of activity across a large distributed neuronal population during syncope. Finally, ablating NPY2R VSNs specifically abolished the BJR. Taken together, our findings showed anatomical features of NPY2R VSNs and their influence on physiology, downstream brain networks, and behavior. The precise control of the distinct VSN population across the

whole body offers new insights for studying syncope related conditions and further exploring brain-body interactions.

Disclosures: **J. Ma:** None. **J.W. Lovelace:** None. **S. Yadav:** None. **S. Ugochukwu:** None. **K. Chhabria:** None. **H. Shen:** None. **Z. Pang:** None. **T. Qi:** None. **Y. Zhang:** None. **T. Vaissière:** None. **S. Tan:** None. **G. Rumbaugh:** None. **L. Ye:** None. **D. Kleinfeld:** None. **C. Stringer:** None. **V.M. Augustine:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.13/K8

Topic: F.06. Autonomic Regulation

Title: Role of the posterior insular cortex in cardiorespiratory interoception during fear

Authors: *C. WEIAND[1,2], E. CHO[1], A. RESSLE[1], C. LOVELLA[3], B. SCHMID[1], V. SPOORMAKER[4], N. GOGOLLA[1];
[1]Emotion Res. Dept., Max Planck Inst. of Psychiatry, Munich, Germany; [2]International Max Planck Research School for Translational Psychiatry, Munich, Germany; [3]Ludwig Maximilian Univ. of Munich, Munich, Germany; [4]Genes and Envrn., Max Planck Inst. of Psychiatry, Munich, Germany

Abstract: Interoception comprises sensing, interpretation, integration and regulation of internal signals of an individual (Chen et al, 2021). The first relay site of interoception in the brainstem is the nucleus of the solitary tract (NTS), which receives internal bodily signals. These visceral signals also reach cortical levels, especially the viscerotopically organized (Cechetto, Saper, 1987) posterior ‘visceral’ insular cortex (pInsCtx). The pInsCtx receives and regulates signals from outside as well as inside the body (Craig, 2002, 2003; Critchley et al, 2004) and is involved in predictions of internal states (Livneh et al, 2020). Human studies have shown that emotions are influenced by the perception of bodily signals (Critchley, Garfinkel, 2017). In this context, cardiac interoceptive awareness and respiratory interoceptive accuracy has been found to be predictive of anxiety symptoms (Garfinkel et al, 2016). However, there is little mechanistic understanding of how cardiac and respiratory signals influence emotion. This study focuses on characterizing how cardiac and respiratory signals affect neuronal activity within the pInsCtx and the NTS during fear. We employed viral tracings to map the anatomical connectivity between the InsCtx and the brainstem. We show that InsCtx is reciprocally connected with several brain regions that are involved in cardiorespiratory regulation during arousal. Additionally, excitatory neurons of all sub-divisions of the InsCtx send direct projections to the NTS. These results indicate a possible direct influence of InsCtx activity on autonomic regulatory hubs in the brainstem. We further assessed neuronal and physiological responses to fear in freely moving mice. Directionality analyses indicate that heart rate provides useful information for forecasting pInsCtx activity during but not outside of fear. Interestingly, breathing rate can’t be used for

forecasting pInsCtx activity during fear acquisition but during fear extinction. Our recordings further show that fear cues as well as fear behavior elicit fear-state dependent alterations in the physiological signals and neuronal activity in both the NTS and the pInsCtx. For example, activity in both recorded regions show increases at on- and offsets of freezing episodes. Freezing is further accompanied by a drop in heart rate, a dominance of the parasympathetic nervous system and a 4Hz breathing rhythm. Further interactions between the modalities are subject of ongoing analyses. Overall, the data suggests that heart and breathing rate play distinct but complementary roles during fear processing which can be further differentiated by their interaction with pInsCtx.

Disclosures: C. Weiand: None. **E. Cho:** None. **A. Ressle:** None. **C. Lovella:** None. **B. Schmid:** None. **V. Spoormaker:** None. **N. Gogolla:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.14/K9

Topic: F.06. Autonomic Regulation

Title: Resting-state BOLD signal measured at 7T indicates autonomic regulation can be traced at the brainstem and cortex

Authors: *J. DEAN, B. AKIN, D. A. HANDWERKER, P. BANDETTINI;
Section on Functional Imaging Methods, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: We investigated autonomic regulation of heart rate (HR) and mean arterial pressure (MAP) in humans using blood oxygen level-dependent (BOLD) signals in resting-state functional MRI (rs-fMRI). BOLD fluctuations are sensitive to changes in neural activity as well as in the localized regulation of blood flow. In this study, we have evidence suggesting brainstem and cortical activation that is potentially involved in the autonomic nervous system to regulate HR and MAP. Healthy adult participants (n=12, 26.4 ± 3.0 years old, 5 females) performed a resting-state task during a 7T multi-band fMRI acquisition (TR=0.75, voxel-size=2mm isotropic). Cardiac and MAP fluctuations were collected concurrently with fMRI using Caretaker (Biopac). Cardiac regressors were computed for each run using AFNI's physio_calc.py tool, facilitating manual examination and adjustment as needed, and then converted to HR. fMRI data were motion-corrected, frequency filtered (0.01-0.1 Hz), and registered to MNI space. A general linear model was applied to each scan. The design matrix included the HR time series and MAP time series. Subject-level activation and t-statistic maps were used to perform a repeated-measures group analysis. Group activation maps were calculated for HR and MAP. Activation to HR is found to be localized in the medulla. In contrast, activation to MAP is localized in the pons. The nuclei concur with brain regions that are part of the autonomic nervous system. Beyond the brainstem, activation to HR is observed near the ventricles, caudate, and cerebellum. In contrast, activation to MAP is observed across the visual cortex and much of the cortical grey

matter. Further study is needed to better differentiate the BOLD signal's source from neural activation or vascular effects, especially in the cortex. There exists a spectrum of conditions involving altered autonomic function, including autonomic cardiovascular disease. In studies that investigate human autonomic regulation, blood pressure is often externally modulated by performing a task or by pharmacologic procedure. While sensitive to multiple noise sources, non-invasive, high spatial resolution rs-fMRI has the potential to be an approach that is easier for clinical data collection, which may facilitate the development of targeted therapeutic interventions in humans with conditions involving altered autonomic function.

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Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.15/K10

Topic: F.06. Autonomic Regulation

Support: CCRYN- Central council of Research in Yoga and Naturopathy, New Delhi, India

Title: Effect of Cardiac Yoga Protocol in CAD Patients and its effect on Inflammatory markers, Clinical and Neuropsychological Parameters

Authors: *S. KUMARI[1], D. DAHIYA[2], A. ANAND[3], D. SINGH[4], D. PANDA[2];
[1]Panjab Univ., Chandigarh, Chandigarh, India; [2]PGIMER, Chandigarh, India; [3]P.G.I.M.E.R, Chandigarh, India; [4]Panjab Univ., Chandigarh, India

Abstract: Effect of Cardiac Yoga Protocol in CAD Patients and its effect on Inflammatory markers, Clinical and Neuropsychological ParametersSwati Kumari[1], Neelam Dahiya[2*], Akshay Anand[3], Gurmeet Singh[4], Prashant Panda[2]PhD Scholar, Interdisciplinary Centre for Swami Vivekananda Studies, Panjab University, ChandigarhAssociate Professor, Department of Cardiology, PGIMER ChandigarhProfessor, Department of Neurology, PGIMER ChandigarhProfessor, Department of Physical Education, Panjab University, ChandigarhProfessor, Department of Cardiology, PGIMER Chandigarh**Corresponding Author:Dr. Neelam Dahiya**Associate ProfessorDepartment of CardiologyPGIMER, ChandigarhEmail-drneelamdahiya@gmail.comContact-+919876386810**Conflict of Interest:** Swati Kumari: None, Neelam Dahiya: None, Akshay Anand: None, Gurmeet singh: None, Prashant Panda:NoneCoronary artery disease (CAD) is one of the world's largest reasons of illness and mortality, especially in developing nations like India. According to WHO estimates, 32 % of all deaths worldwide were due to cardiovascular diseases (CVDs) in 2019. This study aimed to investigate the impact of Yoga on Coronary Artery disease (CAD) patients on inflammatory markers, Clinical and psychological parameters of patients. Total of 100 patients were recruited who have after PCI (Percutaneous Coronary Intervention) after 2-8 weeks aged between 18 to 65 years and having good and fair functional status with LVEF (Left Ventricular

Ejection Fraction) more than 40 %. They were randomly allocated into Yoga and Usual Care group. All the assessments are performed at baseline and after three months. We performed Clinical and psychological assessments and besides measured blood inflammatory markers and lipid profile of the participants. Outcomes were compared with Usual care group who were following the standard medical prescription and intervention group . For clinical assessments we have done TMT (Treadmill Test) and ECG (Electrocardiogram) and HRV(Heart Rate Variability). To assess the psychological assessments, we used WHOQOL scale, PHQ-9, GAD-7 and Yoga Attitude Scale and reported significant improvement in various parameters in intervention group as compared to usual care group. Similarly, inflammatory markers such as IL-6(Interleukin 6), D-dimer and Fibrinogen were also found to have decreasing trend after Yoga intervention. The results indicate that Cardiac Yoga protocol is effective in enhancing the overall quality of life and Yoga attitude in the patients of coronary artery disease enhancing functional status and also decreasing the inflammation associated with CAD.

Disclosures: S. Kumari: None. **D. Dahiya:** None. **A. Anand:** None. **D. Singh:** None. **D. Panda:** None.

Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.16/K11

Topic: F.06. Autonomic Regulation

Support: American Psychological Foundation
University of Iowa Office of Undergraduate Research

Title: Heart rate variability supports emotional intelligence and social competency in schizotypy

Authors: *E. K. WOJCIKOWSKI[1], J. LOPEZ[2], S. AKHRAS[2], T. F. FILIP[3], K. MINOR[4], K. N. THAKKAR[5], A. MCCLEERY[2];
[1]Psychological and Brain Sci., The Univ. of Iowa, Iowa City, IA; [2]Univ. of Iowa, Iowa City, IA; [3]Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA; [4]Indiana Univ. – Purdue Univ. Indianapolis, Indianapolis, IN; [5]Psychiatry, Massachusetts Gen. Hosp., Boston, MA

Abstract: Heart rate variability (HRV) is conceptualized as a physiological marker of adaptive capacity and self-regulation. HRV is associated with social cognitive abilities in non-clinical samples, including emotion perception and emotion regulation (Holzman & Bridgett, 2021; Quintana et al., 2012). HRV is reduced in schizophrenia (Benjamin et al., 2021), a neuropsychiatric condition characterized by marked impairments in social cognition and social functioning. Little is known about HRV along the psychosis continuum, including psychometric schizotypy (SZY), which is typified by subthreshold psychotic-like experiences and is associated with reduced social functioning. Undergraduate students with elevated SZY (n = 44) completed a resting state electrocardiography (ECG) assessment and the Brief Social Skills Inventory (B-

SSI), a self-report measure of emotional intelligence and social competency, including expression of emotion ('Emotion Expression'), higher-level regulation and management of one's emotional states ('Emotion Control'), perception of emotional states of others ('Emotion Sensitivity'), and social adeptness ('Social Control'). HRV was quantified as the root mean square of successive differences (RMSSD) between heartbeats, and was derived for each participant from 8-minute artifact-free epochs of ECG. Associations between HRV and the B-SSI indices were tested with correlations, and direct and indirect relationships among the variables were tested with bootstrapped regressions. HRV was associated with reduced Emotion Expression [r = -.302, p = .046], and marginally associated with enhanced Emotion Sensitivity [r = .294, p = .053]. Emotion Expression was associated with Emotion Control [r = -.408, p = .003], and in turn, Emotion Control was associated with Social Control [r = .334, p = .018]. A serial mediation model provided a good fit for the data, and explained 25.5% of the variance in Social Control [$F(3,40) = 4.564$, p = .008, R^2 = .255]. The indirect effect from HRV to Social Control via Emotion Expression and Emotion Control was significant [B = .074, boot 95% CI: .004, .176], indicating that HRV influenced self-reported social adeptness via modulation of the expression and management of one's emotional states. Limitations of this study include the cross-sectional nature of the data and reliance on self-report measures rather than performance-based or clinician rated measures of socio-emotional processes. These data indicate that autonomic regulation supports emotional intelligence and social competency in emerging adults with elevated SZY, and point to HRV as a modifiable target to enhance social skills in this population.

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Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.17/K12

Topic: F.06. Autonomic Regulation

Title: The Role of Stochastic Resonance in Enhancing Psychophysiological Responses to Music and Modulating Autonomic Nervous System Function

Authors: *K. DIAZ LOZANO[1], O. BECERRA CASILLAS[2], B. DE LA TORRE[3];
[1]Univ. de Guadalajara, Mexico, Mexico; [2]Univ. de Guadalajara, Zapopan, Mexico; [3]Computer Sci., Univ. de Guadalajara, Guadalajara, Mexico

Abstract: The Role of Stochastic Resonance in Enhancing Psychophysiological Responses to Music and Modulating Autonomic Nervous System Function The inclusion of stochastic noise in systems can trigger resonance, thereby amplifying desired responses within the system. This phenomenon, known as stochastic resonance, reveals that stochastic noise can have

constructive effects by inducing new ordered patterns, amplifying weak signals, and enhancing system performance.The study focused on investigating how stochastic noise can influence physiological responses associated with psychosocial well-being in response to auditory stimuli. Emphasis was placed on facilitating alpha and theta brain states, as well as modulating the autonomic nervous system, reflected in heart rate variability. The latter is considered a key indicator of autonomic nervous system modulation, representing the net effect of the parasympathetic nervous system (which decreases heart rate) and the sympathetic nervous system (which accelerates it).To conduct the study, an experimental protocol was implemented with adults of both genders, aged between 19 and 25 years. These participants were exposed to an auditory stimulus consisting of a low-tempo musical piece, over which different levels of stochastic noise were superimposed. During this process, their electro-physiological signals, both from the heart and the brain, were recorded. The main objective was to identify one of these noise amplitudes, referred to as "optimal noise," that stood out from the others, thus generating resonance and amplifying the desired phenomenon.Preliminary results demonstrate the feasibility of modulating the magnitude and interval of physiological responses to auditory stimuli, promoting synchronization between the central nervous system and the cardiovascular system. It is important to understand how stochastic noise can influence the modulation of heart rate variability and the induction of brain states in the alpha and theta bands, as this could offer new avenues to address stress and other psychophysiological challenges in modern society.

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Poster

PSTR036: Cardiovascular Regulation and Integration

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.18/K13

Topic: F.06. Autonomic Regulation

Support: OD025349

Title: Curating collaborative knowledge: SPARC.science an NIH approved multi-consortia data repository in neuroscience and systems physiology

Authors: A. PILKO[1], T. GILLESPIE[2], B. PATEL[3], S. TAPPAN[4], M. PELA[5], J. K. BOLINE[6], J. S. GRETHE[7], J. B. WAGENAAR[8], ***A. BANDROWSKI**[1], M. E. MARTONE[9];
[1]UCSD, La Jolla, CA; [2]Neurosci., UCSD, San Diego, CA; [3]California Med. Innovations Inst., San Diego, CA; [4]Rock Maple Sci., Hinesburg, VT; [5]ABC, ABC, CA; [6]Informed Minds Inc, Walnut Creek, CA; [7]Neurosciences, Ctr. for Res. in Biol. Systems, Univ. of California San Diego, La Jolla, CA; [8]Dept. of Biostatistics, Epidemiology and Informatics, Univ. of Pennsylvania, Rutledge, PA; [9]Neurosci., UCSD, La Jolla, CA

Abstract: As part of the NIH Common Fund’s Stimulating Peripheral Activity to Relieve Conditions (SPARC) project, we have developed the SPARC data repository as a FAIR and open

repository to facilitate collaborative research in neuroscience and systems physiology. SPARC's initial focus was mapping neuroanatomical connectivity and physiology of the autonomic nervous system. Over time the scope has expanded to the peripheral nervous system and end-organs. Due to this broad scope in both subject and techniques, SPARC infrastructure accommodates a wide variety of experimental and computational data.
Since SPARC became an open data repository in 2023 it has been selected to support the needs of other consortia. These include HEAL RE-JOIN and PRECISION HEAL. Moreover, SPARC is now a preferred data repository for the broader NIH HEAL Initiative. In addition, individual research groups have chosen to use SPARC to highlight their experiments and fulfill the NIH data sharing mandate.
To ensure datasets on SPARC are well-understood and accessible, data submitted to SPARC follow SPARC standards; including the SPARC Dataset Structure (SDS) and SPARC Minimal Information Standard (MIS) (these allow knowledge graph queries). SDS 2.0 has been endorsed as a data standard by the International Neuroinformatics Coordinating Facility, INCF.org. SPARC actively collaborates with multiple consortia to ensure alignment with consortia specific standards and effective integration into the repository. Each SPARC dataset includes structured metadata files, predictable folder structure, documentation, and detailed protocols. This data structure effectively handles complex datasets spanning various species, experimental techniques, organ systems, and spatial scales. The data platform underlying the SPARC Portal; Pennsieve, supports these efforts by providing robust data upload, storage, and publication capabilities.
Here we present an overview of the human curation and automated processes that enable collaborative knowledge sharing in SPARC. Beyond the technical aspects of curation, we present our experience about the importance of considering human factors when interacting with complex data standards. One part of the solution we have found is to provide personalized assistance via the curation team’s office hours. To enable our curation team and users to focus on the scientific content of the data, it has been critical to have software tools that simplify many of the otherwise complex and tedious tasks of data management. These include the SODA tool, the sparcur pipelines, Microfile+, and the SDS viewer.

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Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.01/K14

Topic: F.08. Food and Water Intake and Energy Balance

Support: FONDECYT Grant Nº 120–0474
DIUV-CI Grant N°01 (CENFI)
ANID Grant 21210295

Title: Anorectic treatments for obesity increase consumption of a high-fat diet during re-feeding in Sprague Dawley rats.

Authors: *M. COVARRUBIAS[1,2], T. DIB[1,3], I. BRAVO[1], R. SOTOMAYOR-ZÁRATE[1]; [1]Ctr. de Neurobiologia y Fisiopatologia Integrativa (CENFI), Inst. de Fisiologia, Facultad de Ciencias, Univ. de Valparaiso, Valparaiso, Chile; [2]Programa de Doctorado en Ciencias mención Neurociencia, [3]Programa de Magíster en Ciencias Biológicas mención Neurociencia, Univ. de Valparaiso, Valparaiso, Chile

Abstract: Obesity has become a severe public health problem worldwide, especially in industrialized countries, due to the widespread availability of highly processed foods that are rich in fat and sugar. In this context, some pharmacological treatments have shown high effectiveness in reducing body weight, especially drugs with an anorectic effect, such as liraglutide and phentermine. However, the effects of these treatments on food preference and the selection of different types of food have not yet been well described. To test this, we induced obesity by exposing male and female Sprague Dawley rats at post-natal day (PND) 21 to a high-fat diet plus 5% sucrose solution (HFD+S) for six weeks, while the control group was fed with chow food plus water. At PND 62, all the animals were exposed to a re-feeding test where they could choose between chow food or a high-fat diet. Then, we performed a dietary and pharmacological treatment for 10 days where all groups were fed with chow food plus water and were daily injected with saline (1 mL/kg i.p), liraglutide (0.05 mg/kg), or phentermine (30 mg/kg). The re-feeding test was performed again at the end of the treatment on PND 74. The results indicate that both anorectic treatments at the indicated doses effectively reduced fat content, although phentermine treatment was better at reducing body weight. In the re-feeding test at PND62, the animals in the control group showed a high preference for chow food, while animals in the HFD+S group showed no preference between both types of food. However, after performing the test following the treatment, the males of the HFD+S group exposed to phentermine or liraglutide showed a significant preference for high-fat food compared to those exposed to saline. In conclusion, these pharmacological and dietary treatments effectively reduced corporal parameters of obesity. However, they also induced an increase in the consumption of high-fat food after fasting, which could eventually lead to a rebound effect. Parameters in brain areas involved in feeding control must be evaluated to understand the underlying mechanism of this behavior.

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Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.02/K15

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH BRAIN Initiative 1RF1MH120144-01
AHA Grant 24PRE1200949

Title: Influence of Prandial States and External Stimuli on GLP-1 Dynamics and Calcium Signaling in the Paraventricular Nucleus

Authors: *F. LUO[1], L. WANG[2], V. R. MIRABELLA[3], R. SAVANI[4], Y. LU[5], M. A. ROSSI[6], Z.-P. PANG[7];
[1]Rutgers, The State Univ. of New Jersey, Piscataway, NJ; [2]Child Hlth. Inst. of New Jersey, New Brunswick, NJ; [3]Neurosci. and Cell Biol., Child Hlth. Inst. of NJ, Rutgers-Rwjms, New Brunswick, NJ; [4]Child Hlth. Inst. of NJ, New Brunswick, NJ; [5]Neurosci., Rutgers, The State Univ. of New Jersey, New Brunswick, NJ; [6]Rutgers Univ. - RWJMS, New Brunswick, NJ; [7]Child Hlth. Inst. of New Jersey, Rutgers Univ., New Brunswick, NJ

Abstract: Obesity and related diseases present significant health challenges that necessitate an in-depth understanding of the neural mechanisms controlling feeding behavior. Our research focuses on the dynamic regulation of glucagon-like peptide-1 (GLP-1) within the paraventricular nucleus (PVN), a pivotal brain region associated with energy balance and stress responses. Utilizing fiber photometry alongside in vivo two-photon calcium imaging with genetically encoded calcium sensors and novel GLP-1 sensors developed in our lab, we aim to elucidate the complex interactions between pre-synaptic calcium dynamics and post-synaptic neuronal activity under various conditions, including different prandial states and external stimuli. We have successfully characterized these novel GLP-1 sensors both in vitro and in vivo, demonstrating their capability to dynamically detect GLP-1 levels in living animals. Our preliminary findings reveal that different prandial states significantly influence the GLP-1 level in the PVN, alongside notable changes in the dynamics of GLP-1R neurons induced by stress and auditory stimuli, potentially offering new insights into how sensory and emotional factors impact eating behavior and energy regulation. This research is poised to enhance our understanding of central GLP-1 pathways and foster the development of targeted interventions for obesity and its comorbidities.

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Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.03/K16

Topic: F.08. Food and Water Intake and Energy Balance

Support: CAPES/Process: 88887.899778/2023-00

Title: Pharmacological activation of GPR139 by TAK-041 modulates energy balance and hypothalamic inflammation

Authors: *E. DOS SANTOS ALVES[1], G. BATITUCCI[2], N. P. MARIN[3], I. V. DE SOUSA CAVALHEIRO[4], N. FERREIRA MENDES[3], L. A. VELLOSO[5];
[1]Dept. of Med. Pathophysiology, Sch. of Med. Sciences, Univ. of Campinas, Campinas, Brazil; [2]UNICAMP - Univ. of Campinas, Campinas, Brazil; [3]Sch. of Med. Sci., Campinas, Brazil; [4]Univ. of São Francisco, Campinas, Brazil; [5]Intrnl. Med., Unicamp, Campinas, Brazil

Abstract: The hypothalamus plays a central role in regulating the body's energy balance. Excessive saturated fat intake triggers an inflammatory response in the hypothalamus, leading to critical functional and structural changes, affecting food intake and energy expenditure. Global obesity rates are rising, prompting the search for new treatments. G protein-coupled receptors (GPCRs) have emerged as potential obesity treatment targets. Inhibiting GPR139 in rodent hypothalamus has been shown to reduce obesity. The development of the selective GPR139 agonist, TAK-041, offers a promising new therapeutic approach for obesity and its associated conditions. Therefore, the aim of this study is to investigate and evaluate the impact of pharmacological activation of GPR139 on the energy balance of mice. Here we employed a diet-induced obesity model, where 6-week-old male C57BL/6J mice fed a high-fat diet for 6 weeks. Then, these mice were divided into four groups (n=3-5): TAK-041, which was treated orally (3 mg/kg/day), semaglutide, treated intraperitoneally (0.5 mcg/g/week), combination therapy (TAK+SEMA) for 4 weeks, and the vehicle. Glycemic metabolism was assessed by glucose tolerance test, hypothalamic gene profile by RT-qPCR, and energy expenditure by indirect calorimetry. The Ethics Committee on the Use of Animals (CEUA) of the University of Campinas approved the experimental protocols (6273-1/2023). Our data indicate that the TAK+SEMA group showed reduced body weight and adiposity, alongside lower food intake and higher energy expenditure. This was supported by decreased hypothalamic gene expression of *nlrp3*, that plays a key role in regulating the innate immune system and inflammatory signaling, *tlr4*, that is a transmembrane protein involved in immune responses to lipopolysaccharides (LPS) and saturated fatty acids (SFAs) and *cx3cr1*, an important chemokine receptor expressed by microglia. Conversely, treatment with TAK-041 alone increased glucose tolerance compared to semaglutide or combined therapy, without affecting body mass. Additionally, the TAK-041 group exhibited increased expression of hypothalamic mRNA of *Il-6*, an interleukin important in inflammation and neurogenesis. Taken together, our data reveal that activating of GPR139 by TAK-041 modulates body mass and glucose metabolism, and regulates hypothalamic gene expression of genes involved in high-fat diet-related inflammation and immune activation. Combining TAK-041 with semaglutide enhances these effects, showing promise for treating obesity and its complications. However, further research is necessary to understand the mechanisms and safety of this treatment.

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Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.04/K18

Topic: F.08. Food and Water Intake and Energy Balance

Title: Monitoring neuronal networks in vitro to predict efficacy of anorectic neuropeptides

Authors: *B. ALTAS[1], G. BRUSCHETTA[2], A. BUZZANCA[2], J. M. DOERR[3], D. LAM[4], K. A. LINCOLN[2], A. PEKCEC[6], H. WAGNER[5], V. MACK[6];
[1]CardioMetabolic Dis. Res., Boehringer Ingelheim GmbH & Co. KG, Biberach an der Riss, Germany; [2]CardioMetabolic Dis. Res., Boehringer Ingelheim Pharma GmbH & Co. KG, Ridgefield, CT; [3]Target Discovery Sci., [4]Global Computat. Biol. and Digital Sci., [5]Dept. of Drug Discovery Sci., Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; [6]CardioMetabolic Dis. Res., Boehringer Ingelheim Pharma Gmbh & Co. KG, Biberach an der Riss, Germany

Abstract: Obesity is considered a serious and rapidly escalating global health crisis, primarily attributed to an imbalance between caloric intake and energy expenditure. Current treatments mainly utilize anorexigenic peptides such as GLP-1 and GIP receptor agonists. The physiological response of these peptides in the hypothalamus is mediated by specific neuronal clusters of the arcuate nucleus, which harbors a complex neuronal network that plays a crucial role in modulating satiety and hunger signaling. Therefore, elucidating the neuronal responses in the arcuate nucleus is essential for characterizing the mode of action of anorectic compounds and and assessing the therapeutic value of new combinations, to discover innovative and highly efficacious anti-obesity medications. Here, we have established an opto-neurophysiology setup that merges functional calcium imaging and electrophysiological recordings in acute brain slices. We make use of chemical calcium indicators to mark neuronal populations within the arcuate nucleus and have successfully captured distinct neuronal responses to various neuropeptides within an appropriate assay window. Our platform allows for sequential monitoring of individual or combined neuropeptides *in vitro*, allowing for differentiation of compounds on a neuronal network level. Lastly, we provide evidence that the selection of differential combinations through such screening leads to greater efficacy in reducing food intake and body weight loss *in vivo*. Therefore, our approach not only determines a pharmacological signature in acute brain slices but also provides a means to predict efficacious combinations for advanced anti-obesity treatment based on synergistic mechanisms.

Disclosures: B. Altas: A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH and Co. KG. **G. Bruschetta:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **A. Buzzanca:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **J.M. Doerr:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **D. Lam:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **K.A. Lincoln:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **A. Pekcec:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **H. Wagner:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **V. Mack:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG.

Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.05/K19

Topic: F.08. Food and Water Intake and Energy Balance

Support: DK133818 (DD)
IOS-1754878 (MJP)

Title: Vasopressin deficiency enhances central GLP-1-mediated suppression of fluid intake in the Brattleboro rat

Authors: *S. A. DAVID[1], D. J. BRAKEY[2], M. J. PAUL[1], D. DANIELS[3];
[1]Psychology, Univ. at Buffalo, Buffalo, NY; [2]Biol. Sci., Univ. at Buffalo, Buffalo, NY; [3]Dept. of Biol. Sci. and Ctr. for Ingestive Behavior Res., Univ. at Buffalo, Buffalo, NY

Abstract: Physiologically and behaviorally, fluid and food intakes are entangled. There is overlap in the brain regions that control the two types of ingestive behavior, and signaling peptides that affect one often affect the other. For example, glucagon-like peptide-1 (GLP-1) suppresses both food intake and fluid intake. The vasopressin-deficient Brattleboro rat has emerged as a potential model organism to separate fluid intake from food intake and could help isolate brain regions particularly involved in fluid intake control. Brattleboro rats drink copious amounts of water, but eat a similar amount of food when compared to wildtype rats. Brattleboro rats are hypersensitive to the fluid intake suppression caused by central administration of a GLP-1 receptor (GLP-1R) agonist, exendin-4 (Ex4), with no differences in sensitivity to the food intake effects. To evaluate if the hypersensitivity is directly related to the untreated vasopressin deficiency in these rats, we implanted osmotic mini pumps containing desmopressin (ddAVP, a vasopressin type 2 receptor agonist) and tested for fluid intake suppression by central administration of Ex4. We found that ddAVP reduced, but did not completely prevent, the hypersensitivity to Ex4, suggesting both correctable and uncorrectable changes underly the response to Ex4. We also found that acute treatment with tolvaptan (a vasopressin type 2 receptor antagonist) in wildtype rats does not produce the hypersensitivity to Ex4 observed in Brattleboro rats. Future experiments are needed to test if Ex4 hypersensitivity develops after more chronic tolvaptan treatment. Together with previous work, these data provide useful context that will help identify the underlying cause of the different responses to Ex4.

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Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

Location: MCP Hall A

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Program #/Poster #: PSTR037.06/K20

Topic: F.08. Food and Water Intake and Energy Balance

Support: Fondecyt 1221508

Title: Unveiling HCAR2 Receptor in Neurons of the Arcuate Nucleus

Authors: *V. SEPULVEDA[1], M. GARCIA ROBLES[2], L. AGUAYP[3];
[1]Cell Biol., Univ. de Concepcion, Concepcion, Chile; [2]Cell Biol., Univ. of Concepcion, Concepcion, Chile; [3]Univ. de Concepción, Concepcion, Chile

Abstract: Introduction: β-hydroxybutyrate (βHB) is the main ketone body that rises during fasting, exercise, or ketosis. Our laboratory recently demonstrated that tanycytes express AMPK-dependently βHB, supporting the notion that these cells act as hypoglycemia sensors. βHB is the endogenous agonist of HCAR2 (GPR109A), a Gi/o protein-coupled receptor. Its localization in adipose tissue, liver, kidney, and others has been identified. However, brain localization of HCAR2, including the hypothalamus, is still unresolved. We previously showed that βHB induced a membrane hyperpolarization in POMC neurons and increased food intake. Because tanycytes can release βHB, understanding HCAR2 localization and its impact on appetite-regulating neurons is necessary.**Material and Methods:** We employed coronal slices of C57BL6 mice to characterize the presence of HCAR2 in various brain regions using in situ hybridization (ISH), immunofluorescence, western blot and qPCR assays. To assess the specific expression of HCAR2 in the hypothalamic region, we colocalize it with glial and neuronal markers in transgenic POMC-eGFP and NPY-eGFP mice. We used cell sorting and qPCR to examine the expression of HCAR2 in NPY neurons. To confirm that the neuronal inhibition previously observed in POMC neurons is attributable to HCAR2 receptor activation, we conducted patch clamp assays on slices using pharmacological inhibitors. **Results:** We examined HCAR2 expression in several brain regions, detecting it in the cortex, hippocampus, cerebellum, and hypothalamus. We demonstrated its colocalization with NPY and POMC neuron populations in the arcuate nucleus. Cell sorting and qPCR allowed us to show that NPY and POMC neurons expressed good levels of HCAR2. Additionally, we demonstrate that POMC hyperpolarization resulted from HCAR2 activation by βHB. **Discussion:** As βHB presents a potent orexigenic effect, we can hypothesize that local synthesis of βHB by tanycytes can directly stimulate NPY neurons via extracellular βHB signaling during fasting periods. However, how HCAR2 a Gi receptor could activate NPY neurons is an event that required further studies.
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Disclosures: V. Sepulveda: None. **M. Garcia Robles:** None. **L. Aguayp:** None.

Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

Location: MCP Hall A

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Program #/Poster #: PSTR037.07/K21

Topic: F.08. Food and Water Intake and Energy Balance

Support: FONCyT- PICT2019-3054 and PICT2020-3270

Title: Binding of LEAP2 to GHSR in the mouse brain induces a long-term inhibitory effect on food intake

Authors: *L. GIOVANINI[1], F. HEREDIA[2], F. BARRILE[2], M. PERELLO[2];
[1]Neurophysiol., IMBICE (Multidisciplinary Inst. of Cell Biology), La Plata, Buenos Aires, Argentina; [2]Lab. of Neurophysiology-Multidisciplinary Inst. of Cell Biol., La Plata, Argentina

Abstract: Liver-expressed antimicrobial peptide 2 (LEAP2) is a newly discovered endogenous ligand of the growth hormone secretagogue receptor (GHSR), a G-protein coupled receptor mainly expressed in the brain that is strongly implicated in the regulation of energy balance. In humans and rodents, LEAP2 is mainly produced in the jejunum and liver, and its plasma levels increase after food intake and decrease in conditions of energy deficit. LEAP2 acts as an antagonist of GHSR blocking the effects of ghrelin, a stomach-derived peptidic hormone with a potent orexigenic effect. LEAP2 plasma concentration is increased in mice and in patients with obesity, in which it correlates with body mass index, fat mass and glycemia, and this increase is thought to be part of an adaptive response to counteract obesity. This is why LEAP2 has recently become a new and very attractive candidate for the development of drugs to treat metabolic disorders. Here, we aim to study the extent to which LEAP2 reaches the central nervous system and the neuronal circuits engaged by LEAP2 to antagonize ghrelin's orexigenic effect. First, we used mice to study the kinetics of the inhibitory effect of LEAP2 on ghrelin-induced food intake. We performed stereotaxic surgeries and we found that the central administration of LEAP2 blocks the orexigenic effect of simultaneously, 1h, 3h or 8h later peripherally administered ghrelin and that this effect lasts less than 24 hours. LEAP2 also inhibits ghrelin-mediated induction of c-Fos in the arcuate nucleus. Moreover, the central administration of LEAP2 diminishes overnight food intake and body weight in mice. Then, we centrally injected fluorescent LEAP2 (F-LEAP2) and animals were perfused at different times. Through fluorescence microscopy, we observed stained neurons, mainly in the arcuate nucleus and strikingly the label remained even after 3 hours. On the other hand, pieces of brain including the hypothalamus were taken and externally incubated with F-LEAP2 to analyze the diffusion and accessibility through the hypothalamus. Surprisingly, we observed that F-LEAP2 has a large diffusion and this seems to be greater than the diffusion achieved by a fluorescent ghrelin analog. We performed in vitro studies in a HEK 293T cell line expressing GHSR in the membrane and we observed that F-LEAP2 remained bound to GHSR for hours. Altogether, our results suggest that LEAP2 reaches the brain easier than ghrelin and that central LEAP2 acutely blocks the orexigenic effect of exogenously administered ghrelin due to a durable binding to GHSR.

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Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

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Program #/Poster #: PSTR037.08/K22

Topic: F.08. Food and Water Intake and Energy Balance

Support: Banting and Best Diabetes Centre
CIRTN-R2FRIC CREATE-NSERC
NSERC

Title: Connecting specific central GLP-1 receptors functionally with glucose homeostasis and energy balance

Authors: *I. SINGH[1], M. S. KUZMENKO[1], L. WANG[3], D. D. BELSHAM[1,2], Z.-P. PANG[4,5], M. WHEELER[1,6];
[1]Physiol., [2]Departments of Obstetrics/Gynecology and Med., Univ. of Toronto, Toronto, ON, Canada; [3]Child Hlth. Inst. of New Jersey, New Brunswick, NJ; [4]Rutgers Univ., New Brunswick, NJ; [5]Child Hlth. Inst. of New Jersy, New Brunswick, NJ; [6]Toronto Gen. Res. Inst., Div. of Advanced Diagnostics, Metabolism Group, Toronto, ON, Canada

Abstract: Central nervous system (CNS) control of metabolism plays a pivotal role in maintaining energy and glucose homeostasis. In the brain, Glucagon-like peptide 1 (GLP-1), encoded by the proglucagon 'Gcg' gene, produced in a distinct population of neurons in the nucleus tractus solitarius (NTS), has been shown to regulate feeding behavior leading to the suppression of appetite. However, neuronal networks that mediate endogenous GLP-1 action in the CNS on feeding and blood glucose are not well understood. This is mainly due to the presence of diverse neuronal subtypes and complex central neuronal connectivity. GLP-1R neurons were found to be broadly distributed in the brain and specific forebrain regions, particularly the hypothalamus, including the arcuate nucleus of the hypothalamus (ARC), received dense NTSGcg neuronal projections. For this reason, the impact of GLP-1 signaling in the ARC, a brain region known to regulate energy homeostasis and feeding behavior was examined. Using a chemogenetic approach, the ARC GLP-1R neurons were activated / inhibited by using Cre-dependent hM3Dq / hM4Di AAV respectively. Under the conditions studied we established that the acute activation of the ARC GLP-1R neurons significantly suppressed food intake while inhibition caused an appetite increase. Importantly, the role of these specific neurons was identified in regulating glucose homeostasis. While inhibition caused glucose intolerance and impaired insulin signaling, the activation didn't cause any changes in their blood glucose levels but presented with an increased insulin secretion. These results highlight the importance of central GLP- 1 signaling within the ARC that express GLP-1R which upon activation, regulates energy and more tightly regulated glucose homeostasis.

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Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

Location: MCP Hall A

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Program #/Poster #: PSTR037.09/K23

Topic: F.08. Food and Water Intake and Energy Balance

Support: 1R01DK132852
2T32DK007563

Title: Weight Regulation by GLP1R agonists via a non-canonical PKA-mTORC1 mediated pathway

Authors: *R. RAGHAVAN[1], T. LE[2];
[1]Vanderbilt Brain Inst., Nashville, TN; [2]Mol. Physiol. and Biophysics, Vanderbilt Univ., Nashville, TN

Abstract: Glucagon-like Peptide-1 Receptor (GLP1R) agonists are approved to treat obesity by reducing food intake and lowering body weight. The molecular mechanism mediating these effects is unknown. Our lab discovered a novel role for mechanistic Target of Rapamycin Complex-1 (mTORC1) contributing to the anorectic effect of GLP1R agonists. Specifically, we show that GLP1R activation increases PKA-mediated phosphorylation of the mTORC1 subunit Raptor at Ser^{791}, and whole-body mutation of Ser^{791} in Raptor attenuates the weight-lowering effect of GLP1R agonists. What these results fail to demonstrate is the cell/tissue type where PKA-mediated Raptor phosphorylation contributes to the anorectic effect of GLP-1R agonists. We hypothesize that proopiomelanocortin (POMC) neurons in the Arcuate Nucleus (ARC) of the hypothalamus contribute to the anorectic effect of GLP1R agonists via PKA-mediated phosphorylation of mTORC1. This is based on preliminary data showing that inhibition of hypothalamic mTORC1 blocks the anorectic effect of GLP1R activation and mice lacking GLP1R expression in POMC neurons are resistant to the anorectic effects of GLP1R agonists. We tested our hypothesis by developing two tamoxifen-inducible Cre-driven mouse lines that either knock down Raptor expression in POMC neurons (iPOMC-Raptor KD) or that replace Ser^{791} with Ala in Raptor in POMC neurons (iPOMC-Raptor KI). Cre induction in both mouse lines also labels POMC neurons with tdTomato with an ~84% efficiency. We observed a ~45% knock down of Raptor in iPOMC-Raptor KD vs. control mice in $tdTomato^{+}$ cells and no difference in Raptor expression between iPOMC-Raptor KD and control mice in $tdTomato^{-}$ cells (n=2/group). To test whether Raptor and the Ser^{791} residue in Raptor in POMC neurons contribute to the anorectic effects of the GLP1R agonist Semaglutide, iPOMC-Raptor KD and iPOMC-Raptor KI mice were fed a 60% high fat diet (HFD) to induce obesity and body-weights were measured during a 14-day Semaglutide treatment period. There was a non-significant tendency for iPOMC-Raptor KD and iPOMC-Raptor KI mice to be less sensitive to the weight-lowering effects of Semaglutide as compared to controls (n=8 group). Although preliminary, our results suggest that POMC Raptor and its Ser^{791} residue contribute in part to the anorectic effect of GLP-1R agonists.

Disclosures: R. Raghavan: None. **T. Le:** None.

Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

Location: MCP Hall A

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Program #/Poster #: PSTR037.10/K24

Topic: F.08. Food and Water Intake and Energy Balance

Title: Hindbrain Glp1r neurons mediate the weight loss of obesity drugs

Authors: *A. ACOSTA;
Monell Chem. Senses Ctr., Philadelphia, PA

Abstract: Hindbrain Glp1r neurons mediate the weight loss effects of obesity drugs
Alisha A Acosta[1], Kuei-Pin Huang[1], Aaron McKnight[1,2], and Amber L Alhadeff[1,2]
[1]Monell Chemical Senses Center, Philadelphia PA 19104 USA[2]University of Pennsylvania, Philadelphia, PA 19104, USA
Long-acting glucagon-like-1 receptor (Glp1r) agonists reduce food intake and body weight in both rodents and humans and are current popular FDA-approved drugs for obesity. Recent studies suggest that these drugs bind Glp1r-expressing neurons that are abundant in the dorsal vagal complex (DVC), arcuate nucleus (ARC), and vagal afferents (nodose ganglion (NG)). However, the Glp1r neuron population(s) that mediates the therapeutic effects of these obesity drugs is unknown. To determine which population(s) contributes to Glp1r agonist-induced anorexia, we ablated Glp1r-expressing neuron populations within the DVC, ARC, and NG, and measured food intake and body weight after administering Glp1r agonists. $Glp1r^{DVC}$ neuron ablation completely blocked the feeding suppression by exenatide and semaglutide (two Glp1r agonist drugs). In a complementary approach, knockout of Glp1r specifically in the DVC (using $Glp1r^{fl/fl}$ mice) similarly blocked food intake suppression by these obesity drugs. In contrast, ablation of $Glp1r^{ARC}$ and $Glp1r^{NG}$ neurons had no effect on the ability for obesity to suppress feeding when compared to controls. To examine long term effects of glp1r agonists on body weight, diet-induced obese mice with neuron ablation were administered semaglutide for three weeks. $Glp1r^{DVC}$ neuron ablation prevented weight loss from treatment with semaglutide. Overall, these data show that $Glp1r^{DVC}$ neurons are necessary for the anorexic and body weight suppressing effects of obesity drugs.

Disclosures: A. Acosta: None.

Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: F.08. Food and Water Intake and Energy Balance

Support: National Brain Research Program (NAP 3.0) of the Hungarian Academy of Sciences

Title: Importance of GLP-1 receptor produced in the orexigenic AgRP/NPY neurons of the arcuate nucleus

Authors: E. VARGA, A. KÁDÁR, G. WITTMANN, *C. FEKETE;
Hun-Ren Inst. of Exptl. Med., Budapest, Hungary

Abstract: The arcuate nucleus (ARC) is known to mediate the effect of the GLP-1 receptor (GLP-1R) agonist anti-obesity drug liraglutide. According to the literature, the orexigenic NPY/AgRP neurons of the ARC do not express GLP-1R and influenced only indirectly by GLP-1R signaling. As we observed GLP-1R expression in a subpopulation of the AgRP/NPY neurons, we examined the significance of GLP-1R expression of these cells. We detected *Glp1r* mRNA expression in 73.53±5.05% of the AgRP/NPY neurons. The GLP-1R agonist Exendin-4 (Ex-4, 1 μM) decreased the firing frequency of the AgRP neurons, but significantly higher level of inhibition was observed when the G-protein inhibitor GDP-β-S was administered intracellularly to the recorded AgRP neuron, suggesting that Ex-4 has direct excitatory effect on AgRP neurons. Indeed, pharmacological inhibition of synaptic inputs unmasked the direct excitatory effect of GLP-1R signaling on these neurons. As the inhibitory effect of liraglutide on food intake decreases gradually during long term administration, we explored the responsiveness of AgRP neurons to Ex-4 in mice treated daily with liraglutide (0.4 μg/g of body weight) for 8 days. Ex-4 increased the firing frequency of AgRP neurons of liraglutide-treated mice. When the G-protein signaling was blocked in the studied AgRP neurons by intracellular GDP-β-S administration, Ex-4 caused marked inhibition of AgRP neurons independently whether the mice received liraglutide pretreatment or not. These data suggest that 8-day liraglutide treatment had no effect on the indirect inhibitory effect of Ex-4 on the AgRP neurons, but markedly increased the direct excitatory effect of GLP-1R signaling. Ablation of GLP-1R from the AgRP neurons (GLP-1R-AgRP KO mice) resulted in decreased body weight, decreased lean body mass and a tendency for increased lean body mass normalized fat content in 14-week old mice, indicating that GLP-1R of AgRP neurons has important role in the regulation of body composition. In addition, the loss of GLP-1R from AgRP neurons prevented the effect of 8-day liraglutide treatment on the body weight of mice. In summary, the effect of GLP-1R agonists on the activity of AgRP neurons depends on the balance of direct and indirect effects of GLP-1R signaling on these cells. Direct effects of GLP-1R signaling on AgRP neurons play important role in the regulation of body composition and mediating the therapeutic effects of liraglutide.

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Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.12/K26

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: R01 DK136284
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DK135212
MH133228

Title: The role of hypothalamic non-Leptin receptor GABAergic neurons in the development of leptin resistance

Authors: H. LI[1], ***Y. XU**[1], Q. TONG[2];
[1]Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [2]IMM, Univ. of Texas Hlth. Sci. Center, Houston, Houston, TX

Abstract: In both rodents and humans, brain leptin signals, predominantly mediated by GABAergic neurons, are crucial for regulating energy homeostasis. It is well-established that obese subjects exhibit high levels of circulating leptin and show insensitivity to leptin treatment, one phenomenon defined as leptin resistance, which significantly limits leptin's clinical utility in treating obesity. However, the neural mechanisms underlying the development of leptin resistance in obesity are still not fully understood. Our previous study showed that chronic activation of GABAergic neurons in the arcuate nucleus (Arc), which contains subsets both expressing and not expressing leptin receptors (LepR), leads to massive obesity. Conversely, specific inhibition of these neurons reduces age-related weight gain and corrects obesity in leptin-deficient *ob/ob* mice, suggesting a critical role for Arc non-LepR neurons in obesity development. Upon challenging with a high fat diet (HFD), our current study found that both LepR and non-LepR neurons in the Arc are activated, with more pronounced activation in the non-LepR ones. We also observed that specific activation of Arc non-LepR GABAergic neurons leads to marked obesity, while leptin treatment only mildly ameliorates this obese phenotype. Although there is no noticeable effect on body weight under normal chow conditions, specific silencing of Arc non-LepR GABAergic neurons significantly attenuates obesity development in response to an HFD challenge. Notably, their chronic inhibition substantially reduces body weight gain in mice with HFD-induced obesity. Altogether, our findings indicate that hypothalamic non-LepR GABAergic neurons play a critical role in regulating the development of obesity, and their aberrant activation may directly contribute to the emergence of leptin resistance.

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Poster

PSTR037: Central Regulation by Leptin, Incretin, and Peripheral Signals

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Program #/Poster #: PSTR037.13/K27

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: R01 5R01AG050598-04
Merlin Foundation

Title: Hippocampal insulin: comparison of in vivo sampling methods and measurements across behavioral testing and repeated hypoglycemia

Authors: *S. DOUGLASS[1], T. R. BUDDHAVARAPU[2], A. J. SMITH[2], S. LEE[2], J. REITANO[3], C. LEVINE[4], E. C. MCNAY[2];
[1]Psychology, State Univ. of New York At Albany, Albany, NY; [2]Behavioural Neurosci., Univ. at Albany, Albany, NY; [3]Ohio State Univ. Col. of Med., Columbus, OH; [4]Neurosci. Inst., Georgia State Univ., Atlanta, GA

Abstract: Insulin has widespread actions within the brain, including energy homeostasis, modulation of feeding, and as a key component of memory processes. Further, brain insulin dysfunction correlates with Alzheimer's disease and other neurodegenerative disorders. However, to this point, measurement of hippocampal insulin has been limited. Determining *in vivo* hippocampal insulin levels both at a healthy baseline and after, e.g., induction of a disease state or in response to cognitive challenge, is essential to advance our understanding of both insulin's procognitive actions and to guide potential therapeutic interventions. We first sought to establish a sampling technique for insulin within awake and moving rats that would minimize tissue damage and maximize accuracy of measurements. We compared microdialysis (MD) to cerebral open flow microperfusion (cOFM) in dual-cannulated 15-week-old male and female Sprague Dawley rats (n=10/sex), taking simultaneous measurements counterbalanced across the hippocampi. Insulin sampling was comparable between probe types. However, gliosis measured using a combination of immunohistochemical markers for GFAP, TMEM-119, and CD68 was higher around the cOFM probes. Hence, we used MD for subsequent experiments. Basal extracellular hippocampal insulin was found to be 0.3 ng/mL +/- 0.02 ng/mL (n=8). We were then able to show that both a disease state (recurrent hypoglycemia) and a cognitive task (spontaneous alternation) altered hippocampal insulin in male and female 15-week-old Sprague Dawley rats (n=7-8/group). For the first time, we confirmed that hippocampal insulin levels fluctuate acutely and chronically across conditions. Our data constrain mechanisms by which insulin can modulate hippocampal function and offer guidance for future clinical approaches.

Disclosures: S. Douglass: Other; BASi Research Products. **T.R. Buddhavarapu:** None. **A.J. Smith:** None. **S. Lee:** None. **J. Reitano:** None. **C. Levine:** None. **E.C. McNay:** None.

Poster

PSTR038: Processing Threats and Pain

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.01/K28

Topic: G.04. Emotion

Title: Cell-type specific modulation of fear expression to ambiguous and explicit threat in the central amygdala

Authors: *C. DEMAESTRI[1], J. MAGUIRE[2];
[1]Tufts Univ. Sch. of Med., Boston, MA; [2]Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Anticipating and appropriately responding to potential danger is critical for survival. However, excessive anticipation especially in the absence of immediate threat can significantly impair daily functioning. Exaggerated fear responding is a hallmark of fear and anxiety-related disorders and in part stems from hyper-responsivity to threat predictive cues and inability to flexibility update behavioral responses. Recent advancements have demonstrated that distinct neural subtypes in the lateral central amygdala (CeAL) play a modulatory role in the expression of passive and active fear states. Namely, CeA neurons expressing the neuropeptide corticotropin-releasing factor (CRF+) promote the active expression of flight and neurons expressing somatostatin (SOM+) promote the passive expression of freezing. However, a large portion of this work has focused on conditioned stimuli (CS+) that immediately precede the unconditioned threatening stimulus. Therefore, less is known about how the CeAL encodes threat-predictive information under conditions of uncertainty and how different populations of neurons cooperate to enact an appropriate behavioral response. Here, we demonstrate that adult mice comparably acquire a conditioned freezing response to a CS+ that immediately precedes a shock (explicit CS+) compared to a CS+ associated with varying timing of shock (ambiguous CS+). Subsequent re-exposure to the CS+ revealed high levels of freezing to the explicit CS+ and attenuated freezing to the ambiguous CS+. These data indicate that the temporal predictability of a CS+ differentially influences the expression of freezing and raises the possibility that behavioral responses to explicit and ambiguous threat may be differentially driven by CeAL CRF+ and SOM+ neurons. In ongoing work, we use chemogenetics to test the hypothesis that modulating the activity of CeAL CRF+ or SOM+ neurons during recall of explicit and ambiguous CS+ produces opposing shifts in the expression of fear. These studies will lay the groundwork for understanding the neural mechanisms underlying adaptive and maladaptive fear responding.

Disclosures: C. Demaestri: None. **J. Maguire:** None.

Poster

PSTR038: Processing Threats and Pain

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.02/K29

Topic: G.04. Emotion

Support: NIH
HHMI

Title: Population coding of predator identity, imminence, response, valence and scalable defensive state in the hypothalamus

Authors: *Y. CHEUNG[1], A. NAIR[2], L. LI[3], M. G. SHAPIRO[1], D. ANDERSON[1]; [2]Computation and Neural Systems, [1]Caltech, Pasadena, CA; [3]Neurobio., Capital Med. Univ., Beijing, China

Abstract: Innate defensive behaviors enable survival by endowing brains with pre-programmed responses to life-threatening situations. Hypothalamic VMHdm^{SF1} neurons are known to be activated by predator odors and are necessary and sufficient for instinctive defensive responses to predators. However, those data alone do not distinguish whether these neurons primarily encode predator identity, proximity, defensive motor programs or an internal fear-like state. To resolve this issue, we imaged VMHdm^{SF1} neurons at single-cell resolution in freely behaving mice exposed to a natural predator in varying contexts. The largest source of variance in neural activity was explained by the stimulus object (predator vs. toy), with distinct subpopulations encoding object-specific vs. novelty responses. Predator-evoked responses ramped up and down with similar kinetics during approach vs. flight, respectively, but did not scale with absolute distance from the stimulus, suggesting a process of integration followed by slow stimulus-independent decay. Unexpectedly, we discovered a distinct subset of VMHdm^{SF1} neurons activated by entry into a shelter, yielding bi-directional population coding of threatening vs. safe environments. Strikingly, there was little or no representation of defensive motor actions under any conditions, despite the fact that optogenetic stimulation of VMHdm^{SF1} neurons can robustly elicit freezing and flight behaviors. Instead, we identified a subpopulation representing predator imminence and/or context. Finally, we found a strong positive correlation between individual differences in predator defensiveness and the decay rate of predator-evoked activity. Taken together, these data suggest that VMHdm^{SF1} neurons encode both threat object identity, and the intensity (strength) and the dynamics (length) of an internal defensive state, in a context-dependent manner.

Disclosures: Y. Cheung: None. **A. Nair:** None. **L. Li:** None. **M.G. Shapiro:** None. **D. Anderson:** None.

Poster

PSTR038: Processing Threats and Pain

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.03/K30

Topic: G.04. Emotion

Support: NIH Grant K00 MH130162
NIH Grant R01 MH128235

Title: Basolateral amygdala interneuron-driven oscillatory states engage valence-specific ensembles and distinct downstream circuits

Authors: *K. A. AMAYA, J. MAGUIRE;
Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: The binary assignment of positive or negative valence to cues, environments, and outcomes, termed valence processing, is crucial for behavioral approach or avoidance, and thus survival. A critical brain region for valence processing is the basolateral amygdala (BLA), as both appetitive and aversive learning are dependent on BLA function. Recent advances have highlighted the role of interneurons in mediating BLA oscillatory states associated with both positive and negative valence processing, such as fear expression and reward seeking. Despite their documented ability to govern BLA states and relevant behaviors, the involvement of interneurons in ensemble recruitment and information routing to distinct circuits remains unknown. To address this, we conducted a series of experiments aimed at interrogating the ability of BLA interneurons to facilitate valence processing through the recruitment of distinct neuronal ensembles in the BLA and downstream circuits. We first quantified overlap between neurons activated under different valenced states using cFos expression (post fear conditioning or after extinction) and distinct BLA projection populations (targeted using retrograde GCaMP). We then examined the impact of driving the BLA network at specific frequencies associated with negative or positive valence processing (4 Hz or 8 Hz, respectively) using a Dlx-driven channelrhodopsin, on the recruitment of BLA ensembles and retrogradely-labeled projection populations. We conclude by showing that BLA interneuron stimulation at different frequencies engages distinct ensembles in the BLA and downstream brain-wide networks. Together, our results provide a framework to understand BLA valence processing as a product of microcircuit governance over ensemble engagement, oscillatory states, and network activation.

Disclosures: K.A. Amaya: None. **J. Maguire:** None.

Poster

PSTR038: Processing Threats and Pain

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.04/K31

Topic: G.05. Mood Disorders

Support: NIH Grant MH077681
NIH Grant AA027989

Title: Modulation of stress coping responses by the basolateral amygdala

Authors: *A. R. SOARES[1], C. FAI[1], Y. S. MINEUR[3], M. PICCIOTTO[2];
[1]Psychiatry, Yale Univ., New Haven, CT; [2]Dept Pyschiat, Yale Univ., Guilford, CT; [3]Psychiatry, Yale Univ. Sch. Med., North Haven, CT

Abstract: Transition between adaptive and maladaptive coping strategies intersects with shifts in perceived stress controllability and uncontrollability. In addition, passive coping (generally considered maladaptive) is often associated with depression. The basolateral amygdala (BLA)

plays a key role in stress-relevant behaviors, and neuromodulation by norepinephrine (NE) is critical for producing adaptive coping responses. To investigate the role of BLA NE in coping behavior, and how its function changes with the controllability of the stressor, we performed fiber photometric recordings of NE levels in the mouse BLA during behaviors involving escapable and inescapable stress. Escapable stress was modeled by the looming shadow test, in which mice were presented with an expanding disc mimicking a descending aerial predator; in this assay, mice exhibit a passive coping response by freezing, or an active coping response by fleeing into a shelter. Inescapable stress was modeled by the tail suspension test, during which mice transition between bouts of struggling (active coping) and immobility (passive coping). Fiber photometric recordings were carried out using a GPCR-Activation-Based (GRAB) NE sensor. We found that BLA NE was elevated during passive coping to escapable stress, and active coping to inescapable stress, suggesting that NE integrates information about the nature of the escapability of the stressor. We then used oChIEF to optogenetically stimulate NE terminals in the BLA and found that 5 Hz stimulation decreased passive coping to escapable, but not inescapable stress, further highlighting the interaction between NE signaling and stress controllability. This stimulation pattern also inhibited cFos immunoreactivity (used as a proxy for neuronal activation) in the BLA, suggesting that 5 Hz stimulation of NE terminals promotes active coping by inhibiting BLA neurons. The interaction between BLA and LC neurons was further demonstrated by the inverse correlation between cFos immunoreactivity in the LC and the BLA. Although behavioral responses to NE stimulation were consistent across sexes, inhibition of BLA cFos was only observed in males. We will further evaluate the relationships between sex, NE stimulation, and coping behavior with pharmacological and optogenetic manipulations to better understand how BLA neuromodulation mediates stress reactivity.

Disclosures: A.R. Soares: None. **C. Fai:** None. **Y.S. Mineur:** None. **M. Picciotto:** None.

Poster

PSTR038: Processing Threats and Pain

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.05/K32

Topic: G.04. Emotion

Support: 9445905
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9360170
9445905
8730067

Title: Basolateral Amygdala Parvalbumin and Cholecystokinin-expressing GABAergic Neurons Modulate Depressive and Anxiety-like Behaviors.

Authors: *M. ASIM[1,2];
[1]City Univ. of Hong Kong, Kowloon, Hong Kong; [2]Ctr. for Regenerative Med. and Health, Hong

Kong Inst. of Sci. and Innovation, Chinese Acad. of Sciences, Hong Kong., Hong Kong, Hong Kong

Abstract: The basolateral amygdala (BLA) is increasingly recognized as a key regulator of depression and anxiety-like behaviors. However, the specific contribution of individual BLA neurons to these behaviors remains poorly understood. Building on our previous study, which demonstrated increased activity in glutamatergic BLA neurons in response to aversive stimuli and that enhancing inhibition in the BLA can alleviate depressive-like behaviors, we investigated the role of individual GABAergic neurons (BLA^{GABA}) in depressive and anxiety-like phenotypes. To address this question, we employed a comprehensive array of techniques, including c-fos staining, fiber photometry recording, optogenetic and chemogenetic manipulation, and behavior analysis. Our findings indicate that BLA^{GABA} neurons show decreased activity during tail suspension and after chronic social defeat stress (CSDS) during social interaction. High-frequency activation of BLA^{GABA} neurons attenuated depressive and anxiety-like behaviors, while low-frequency activation had no effect. Moreover, aversive stimuli, such as footshocks, increased c-fos activity in BLA GABAergic neurons expressing somatostatin (SST), parvalbumin (PV), and cholecystokinin (CCK). Fiber photometry recordings revealed increased activity in PV and SST neurons and decreased activity in CCK-GABA neurons in the BLA during tail suspension stress. However, after CSDS, BLA^{PV} neurons displayed decreased activity, while SST and CCK neurons showed no changes. Behavioral analysis demonstrated that chemogenetic inhibition of PV and CCK-GABA neurons induced depressive and anxiety-like behaviors, respectively, whereas SST neuron inhibition had no effect. Conversely, chemogenetic activation of BLA^{PV} neurons alleviated depressive behaviors, and activation of $BLA^{CCK\text{-}GABA}$ neurons alleviated anxiety-like behaviors. This study provides compelling evidence for the critical role of BLA^{PV} neurons in regulating depressive behaviors and $BLA^{CCK\text{-}GABA}$ neurons in modulating anxiety-like behaviors in mice.

Disclosures: M. Asim: A. Employment/Salary (full or part-time):; 3Centre for Regenerative Medicine and Health, Hong Kong Institute of Science and Innovation, Chinese Academy of Sciences, Hong Kong., Department of Neuroscience, City University of Hong Kong, Kowloon Tong, Hong Kong., Department of Biomedical Science, City University of Hong Kong, Kowloon Tong, Hong Kong..

Poster

PSTR038: Processing Threats and Pain

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.07/K34

Topic: G.04. Emotion

Support: T32 Grant DA007287
NIH NIDA Grant DA047102
NIH NIDA DA060221

Title: Operant tasks of emotional reactivity: Force and duration of bar pressing are sensitive to distinct psychological constructs

Authors: *Y. MARMOL CONTRERAS[1], T. E. VASQUEZ[2], P. SHAH[3], T. A. GREEN[4]; [1]UTMB, Galveston, TX; [2]Univ. of Texas Med. Br. At Galveston, LEAGUE CITY, TX; [3]The Univ. of Texas Med. Br., Galveston, TX; [4]PharmTox, UT Med. Br., Galveston, TX

Abstract: Despite a strong association between frustration, aggression, and substance use, emotional reactivity is seldom studied in conjunction with motivation-related behaviors. This is partially due to a lack of robust, quantitative assays that can be easily integrated into studies of motivational behaviors. We have recently discovered a cost-effective method for the study of emotional states during operant tasks by monitoring changes in lever interactions. For instance, we validated duration of bar pressing as a robust frustration-related measure during operant tasks. An alternative parameter sensitive to nonreward, force of responding, has been associated with aggression and frustration in human literature. However, until now, force of pressing has not been integrated into operant tasks of animal behavior. In this investigation, we examine force and duration of responding for animals self-administering sucrose or cocaine. We find that the typical increase in duration of pressing during EXT and PR, referred to as the operant frustration effect, was not present for force of pressing. However, we discovered that in a novel frustrative nonreward (FN) paradigm, rats self-administering sucrose also increased force of pressing. We modified this task to assess the role of proximity to reward, effort expenditure, and loss of progress on resulting force and duration of bar pressing in male and female rats, and found force and duration of pressing to be sensitive to distinct psychological constructs. Determination of the precise neurocircuitry involved in controlling changes in duration and force may elucidate the best application for those tools in pre-clinical settings.

Disclosures: Y. Marmol Contreras: A. Employment/Salary (full or part-time):; UTMB. **T.E. Vasquez:** None. **P. Shah:** A. Employment/Salary (full or part-time):; Full-time. **T.A. Green:** A. Employment/Salary (full or part-time):; F.

Poster

PSTR038: Processing Threats and Pain

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.08/L1

Topic: G.04. Emotion

Support: NIH ZIAMH002881
NIH ZICMH002952

Title: Frustrative non-reward induced irritability changes oscillations and neural spiking in the frontal cortex

Authors: *X. MA[1], A. A. NAIK[2], E. LEIBENLUFT[1], Z. LI[3];
[1]NIH, Bethesda, MD; [2]NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD; [3]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Irritability is an emotional state that is conceptualized as a low threshold to experience anger in response to frustration. In children and adolescents, severe irritability is a defining symptom of Disruptive Mood Dysregulation Disorder (DMDD). Chronic irritability during youth also predicts adult anxiety and depression. Despite the long-lasting adverse impact of irritability, little is known about the underlying neural mechanism, and there are no specific therapies for irritability. fMRI and EEG studies in humans show that brain network activities are altered in children with severe irritability. However, it is unclear whether and how these changes are related to irritability. To interrogate the brain regions and brain activities involved in irritability, we used extracellular electrophysiology to record local field potential (LFP) and spiking activities from multiple brain regions in freely moving animals while they are performing a frustrative non-reward behavioral paradigm, a new behavioral paradigm developed by our lab named alternating poking reward omission (APRO). Briefly, mice were trained to alternate between two water dispensers located on the opposite sides of a linear track to get water rewards for 3 days. On day 4, the reward was omitted in 50% trials. Then the omission ratio was increased to 80% on day 5. After APRO, animals showed irritability-like behavior such as restlessness and aggression. We used whole brain c-Fos staining after APRO to identify brain regions that are activated by frustration. Based on the c-Fos data, we chose 8 brain regions as candidate irritability-related regions for in vivo electrophysiology. These regions are orbital frontal cortex (OFC), agranular insular (AI), anterior cingulate cortex (ACC), nucleus accumbens (NAc), mediodorsal thalamus (MDT), CA1, caudate putamen (CPu), and lateral hypothalamus (LH). We designed a micro-drive tetrode array to simultaneously record from the 8 brain regions. Our recording showed that while reward decreases spike rates in the frontal cortex, some frontal cortical neurons increase spike rates in response to reward omission. After animals completed the FNR session and returned to the home cage, gamma-band LFP power in the frontal cortex decreased, suggesting that FNR causes long-lasting effects on frontal cortical activities. These findings suggest that FNR regulates firing of frontal cortical neurons and alters local synchronization of cortical neurons. These changes can impact cortical control of locomotion and aggression to contribute to the behavioral manifestation of frustration.

Disclosures: X. Ma: None. **A.A. Naik:** None. **E. Leibenluft:** None. **Z. Li:** None.

Poster

PSTR038: Processing Threats and Pain

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Program #/Poster #: PSTR038.09/Web Only

Topic: G.04. Emotion

Support: FJNU Research Start-Up Funds

Title: Empirical Support for the Fear Threshold Model: Multimodal Fear Expression in Rodents Facing Ambiguous Threats

Authors: *J. RAO[1], B. YIN[2];
[2]Sch. of Psychology, [1]Fujian Normal Univ., Fuzhou, China

Abstract: The Fear Threshold Model (Bao et al., 2024) posits that animals exhibit distinct fear response patterns based on the perceived certainty of threats. The model predicts a progression from reward-seeking to defensive behaviors and ultimately to subjective fear as threat certainty increases in ambiguous situations. Using a fear conditioning paradigm with generalization tests in rats, we created contexts with varying levels of threat ambiguity, through which we evaluated this model by measuring five behavioral indicators: 50kHz ultrasonic vocalizations (USVs), reward-seeking (lever pressing), freezing, defecation, and 22kHz USVs, which correspond to pleasure, appetitive motivation, defensive response, stress response, and subjective fear, respectively. The Fear Threshold Model predicts that 50kHz USVs and reward-seeking behaviors will be highest in safe contexts and decrease as threat certainty increases. Freezing behavior, driven by subcortical pathways, is expected across various threat levels. Defecation is anticipated to be less influenced by threat certainty and more dependent on imminent threat intensity. 22kHz USVs, which are linked to higher-order processing, should primarily appear in contexts where threats are certain but less imminent and decrease in ambiguous situations. Our results showed that lever pressing was highest in a baseline safe environment and was maintained during the contextual test but significantly declined during fear learning, cued tests, and generalization tests. Freezing was prominent across fear learning, contextual, and cued tests, while 22kHz USVs and defecation were evident only during the fear learning and cued testing phases. In the generalization tests, freezing and defecation showed a gradient decline with increased stimulus differentiation, but defecation displayed greater sensitivity to stimulus differentiation. Meanwhile, 22kHz USVs significantly decreased and even disappeared, except in individuals with high trait anxiety. These findings generally support the Fear Threshold Model, which challenges the simplistic notion that fear expression can be uni-modally measured, adding ecological validity to fear behavior research.

Disclosures: J. Rao: None. **B. Yin:** None.

Poster

PSTR038: Processing Threats and Pain

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.10/L2

Topic: G.04. Emotion

Support: NIH Grant 5R01MH071589

Title: Stages of threat imminence in the human brain

Authors: *V. DINAVAHI[1], L. PESSOA[2];
[1]Psychology, Univ. of Maryland, College Park, MD; [2]Psychology, Univ. of Maryland, Col. Park Neurosci. and Cognitive Sci. Program, College Park, MD

Abstract: We investigated how the human brain dynamically processes different stages of threat imminence with functional magnetic resonance imaging. A virtual predator orbited around the subject's avatar for 10 seconds, with an attack probability of 0%, 10%, or 90% (known to the subject). Attacks resulted in a non-painful but aversive shock and always occurred at the end of the trial. The predator was visible but was not actively attacking during the orbit phase, simulating the "post-encounter phase" of threat-imminence continuum. We analyzed responses during two time windows: early (1.5 to 4.5 seconds after orbit start) and late (-4.5 to 0 seconds before orbit end). We observed a significant effect of attack probability in areas related to attention and emotion processing, like the frontal eye field (FEF), mid and post cingulate cortex (MCC and PCC), anterior dorsal insula, dorsal striatum, and parts of the cerebellum. However, we did not detect an effect for period (early vs. late) by attack probability in these areas, indicating that threat proximity was not a major factor. In addition, we reanalyzed a previous dataset where subjects either avoided a predator or approached a reward (Murty et al., *J Neurosci*, 2023). In this study, the avoidance trials corresponded to the "circa strike" phase of the threat-imminence continuum. We investigated effects of trial period (early vs. late) on responses to threat (high minus low levels) and valence (threat minus reward, averaged separately across high and low levels). We found stronger threat responses in the late compared to early period in attention-related areas (FEF and intraparietal sulcus), ventral striatum (VS), and pulvinar. However, no such differences were found in the MCC or anterior dorsal insula. Instead, we found stronger valence responses in these regions in the late compared to early period. Taken together, our findings suggest that threat imminence is processed by key emotion-related areas when threat is actively attacking (circa strike). Further, the distinction between responses to threat and reward increases especially in the MCC and anterior dorsal insula as the object gets closer (valence-related imminence).

Disclosures: V. Dinavahi: None. **L. Pessoa:** None.

Poster

PSTR038: Processing Threats and Pain

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Program #/Poster #: PSTR038.11/L3

Topic: G.04. Emotion

Support: NIH Grant R21 AT010736

Title: The Potential Role of Prefrontal GABA–Peripheral Immune Interaction in Modulating Pain Catastrophizing in Individuals with Chronic Pain

Authors: *J. MA[1], P. SUBRAMANIAM[1], J. YANCEY[1,2], E. MCGLADE[1,2], P. F. RENSHAW[1,2], D. A. YURGELUN-TODD[1,2];
[1]Diagnos. Neuroimaging/Psychiatry, Univ. of Utah, Salt Lake City, UT; [2]George E. Wahlen Department of Veterans Affairs Medical Center, VISN 19 Mental Illness Research, Education and Clinical Center, Salt Lake City, UT

Abstract: The cognitive-affective components of pain, such as catastrophic thinking about pain and pain-related negative emotions, play a critical role in pain chronicity and disability; however, the neurobiological basis for these pain components has not been fully explored. Additionally, there is a growing interest in the role of neuroimmune interaction in cognitive-affective pain processing. Here, we examined the association between prefrontal brain gamma-aminobutyric acid (GABA) levels and blood markers of peripheral immune activation in individuals with chronic pain. We also explored the separate and combined effects of these brain and immune markers in the cognitive-affective components of pain, including pain catastrophizing. Twenty-five individuals with chronic pain completed a proton magnetic resonance spectroscopy (^{1}H-MRS) scan to assess GABA levels in the anterior cingulate cortex. The neutrophil-to-lymphocyte ratio (NLR) and platelets-to-lymphocyte ratio (PLR) were assessed as markers of peripheral immune activation. We found that higher NLR is associated with lower levels of prefrontal GABA in individuals with chronic pain (β = -0.51, P = 0.02). Both higher NLR and lower prefrontal GABA levels were associated with greater pain catastrophizing (NLR, β = 0.56, P = 0.002; GABA, β = -0.46, P = 0.01). Additional clustering analysis with NLR and prefrontal GABA identified two distinct subgroups (High NLR-Low GABA [n = 16] and Low NLR-High GABA [n = 8]). The High NLR-Low GABA subgroup showed greater pain catastrophizing than the Low NLR-High GABA group (b = 13.8, P = 0.001). Our preliminary data suggest the presence of potential neuroimmune interaction that may play a role in pain catastrophizing. Our finding of the associations between prefrontal GABA level and pain catastrophizing is consistent with previous clinical study results in chronic musculoskeletal pain. Given that pain catastrophizing is a reported factor for chronic pain maintenance and disability, the current findings may have clinical implications. The causal nature of the observed relationships should be clarified in future studies.

Disclosures: J. Ma: None. **P. Subramaniam:** None. **J. Yancey:** None. **E. McGlade:** None. **P.F. Renshaw:** None. **D.A. Yurgelun-Todd:** None.

Poster

PSTR038: Processing Threats and Pain

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Program #/Poster #: PSTR038.12/L4

Topic: G.04. Emotion

Support: NIMH Grant 1R01MH087525-01A2
NIMH Grant MH070539-01
NIDA Grant 1R01DA026505-01A1

Title: Neural representations underlying empathy for pain in female psychopaths

Authors: *J. LI[1], M. S. COHEN[2], H. MA[2];
[1]Univ. of Chicago, Chicago, IL; [2]Univ. of Chicago, Chicago, IL.

Abstract: Empathy is a prerequisite for developing concern for others. In highly psychopathic individuals, however, empathy-elicited concern is largely diminished, alongside perspective-taking and mentalizing capacities. Yet, it remains unclear how such individuals neurologically represent others' distress, and how this representation differs from non-psychopathic counterparts. The current project compares neural activity in regions involved in processing empathy for pain, including the amygdala, ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex (dlPFC), the ventral striatum (VS), and the anterior insula (AI), between an incarcerated sample of highly psychopathic female subjects (N = 17) and low-psychopathy controls (N = 17) during an empathy-for-pain task (EPP). Representational similarity analysis (RSA), an approach which allows for comparisons of brain activity to specific, individual stimuli across conditions, demonstrates that control subjects may be better at identifying whether people are in pain (versus not in pain) than high-psychopathy participants are able. Moreover, RSA revealed that controls represent their own self's pain and other's pain more similarly in empathy-processing regions than highly psychopathic individuals do, indicating a deficit in perspective-taking in this group, corroborated by neural representation patterns. These representational patterns were further examined using multidimensional scaling (MDS), which captures the representational distance between each individual stimulus in a given state space. MDS identified unique clustering patterns between controls and psychopaths in brain regions involved in empathy-for-pain. Together, findings provide empirical evidence for how the distress or pain of another person is neurologically represented by highly psychopathic subjects.

Disclosures: J. Li: None.

Poster

PSTR038: Processing Threats and Pain

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.13/L5

Topic: G.04. Emotion

Title: Neural representations of pain varies across body sites when engaged by attention-demanding task

Authors: *J. A. DAVIS[1], M. SUN[2], T. D. WAGER[3];
[1]Psychological & Brain Sci., Dartmouth Col., Hanover, NH; [2]Psychology and Brain Sci., Dartmouth Col., HANOVER, NH; [3]Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: In the last decade, an explosion of neuroimaging studies have investigated various cognitive strategies of emotion regulation such as reappraisal, acceptance, and distraction. Current brain-based models of emotion regulation implicate the prefrontal cortex (PFC) as

crucial for emotion regulation, specifically the dorsomedial, dorsolateral, and ventrolateral subregions (dmPFC, dlPFC, and vlPFC respectively). During distraction, the presence of attention-demanding tasks such as the n-back or Stroop task during pain stimulation leads to reduced pain intensity and altered neural activity. In attempting to resolve processing competition between task demands and noxious input, the task-irrelevant noxious input becomes suppressed in favor of task demands, allowing participants to perform effectively on the cognitive task. Interestingly, few studies have explored how pain representations differ between different places of stimulation such as the hand, abdomen or legs in relation to these cognitive tasks. If pain representations do differ across body sites, which body sites, all other things being equal, lead to the greatest intensity ratings? Moreover, is pain stimulation easier to suppress when applied to certain body regions over others? Our study used a N of Few design (N = 8) to examine individual differences in both somatotopic and pain representations based on different body areas. Participants experienced heat pain stimuli across 8 different body sites (both arms, both legs, both sides of face, chest and abdomen) while performing an n-back task in the fMRI scanner. We found that participants not only did rate their pain experience as less intense during the high cognitive load condition (2-back), but also rated the left face as less intense overall compared to other sites. We also expect that pain-related neural activation should be altered during the n-back task such that activation in emotion based areas associated with pain such as the anterior insula and ACC should be reduced. Future research should examine how other related cognitive strategies of emotion regulation affect pain stimulation across different body sites.

Disclosures: **J.A. Davis:** None. **M. Sun:** None. **T.D. Wager:** None.

Poster

PSTR038: Processing Threats and Pain

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.14/L6

Topic: G.04. Emotion

Support: Université de Montréal W2024

Title: Are Different Kinds of Subjective Fears Represented Differently in the Human Brain?

Authors: *M. CÔTÉ[1], V. TASCHEREAU-DUMOUCHEL[2];
[1]Dept. of Psychiatry and Addictology, Univ. de Montréal, Montreal, QC, Canada; [2]Psychiatrie et addictologie, Univ. de Montréal, Montréal, QC, Canada

Abstract: The brain mechanisms that generate subjective emotional experiences are still poorly understood. Fear is often considered to be represented similarly in the brain regardless of its origin. However, research suggests that subjective experience may differ depending on the types of memory involved in the experience. For example, previous machine learning studies indicate that decoders of brain activity trained to predict situational fear (semantic information) can

predict the subjective experience triggered by fear patterns (episodic information). However, the reverse does not appear to be true. This finding indicates that fear patterns probably comprise broader brain representations than those generated by situational fear alone. To better understand these differences, we analyzed two fMRI datasets including either experiences of frightening situations (semantic memory) or schema-based fears of animals (episodic memory). By comparing decoder performance in 214 brain regions of the Brainnetome atlas, we identified specific representations of the two types of subjective fear. More specifically, we showed that Fear schemas were predicted more accurately than situational fear in the occipital, superior temporal and prefrontal cortices. Importantly, these results provide valuable information to better understand the brain bases of mental health issues, such as anxiety disorders, that mostly involve incapacitating fear schemas rather than situational fear.

Disclosures: M. Côté: None. **V. Taschereau-Dumouchel:** A. Employment/Salary (full or part-time):; Université de Montréal.

Poster

PSTR038: Processing Threats and Pain

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Topic: G.04. Emotion

Support: NIH grant R01MH076136
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Title: Confirmation bias is generalizable across somatic pain, negative emotion, and cognitive effort

Authors: *A. YAZDANPANAH, H. JUNG, A. SOLTANI, T. D. WAGER;
Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Expectations strongly shape our sensory perception, pronounced in aversive domains such as pain processing. The association between the expectations and what we experience can be flexibly learned via prediction errors which leads to fine-tuned representations of our experience. However, this update could resist change, denoted as “confirmation bias”: learning is strengthened when subjective experience supports expectations, i.e., high learning rate for congruent conditions, and attenuated when the subjective experience contradicts expectations, i.e., lower learning rates for incongruent conditions. Despite prior research on confirmation bias, the existence of shared confirmation bias mechanisms is unknown, due to studies focusing on a single domain. To overcome this, we performed a large study (N = 88) on the effects of expectation on somatic pain, vicarious pain, and cognitive effort within the same participants. Using a combination of model-free and model-based approaches, first, we found that participants update their expectations based on the subjective experience, based on evidence of higher learning rate for congruent conditions and vice versa for incongruent ones, supporting the

existence of confirmation bias across each domain. Moreover, expectancy effects within individuals were highly correlated between somatic pain, vicarious pain, and cognitive effort, pointing out the shared underlying processes necessary for the confirmation biases. Furthermore, we observed some, but not complete, cross-task correlations regarding the confirmation bias in learning rates as well as the stimulus effects, suggesting that, within individuals, sensitivity to stimulus and learning rates are stable between some but not all domains. To further understand the neural mechanism underlying confirmation bias, we aim to find neural correlates of prediction errors and confirmation bias, allowing for further investigation of shared mechanisms of confirmation bias across domains.

Disclosures: A. Yazdanpanah: None. **H. Jung:** None. **A. Soltani:** None. **T.D. Wager:** None.

Poster

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Topic: G.04. Emotion

Support: McDonnell Foundation Small Grant (NM)
R21DA055047 (NM)

Title: Dissecting the accumbal dynorphinergic outputs underlying affective pain

Authors: *F. D'OLIVEIRA DA SILVA[1], H. YOON[2], R. SANDOVAL[3], C. M. CAHILL[4], M. PIGNATELLI[5], N. MASSALY[6];
[1]UCLA, Los Angeles, CA; [2]Washington Univ. In St Louis, Saint Louis, MO; [3]Neurosci., Salk Inst. for Biol. Studies, La Jolla, CA; [4]Psychiatry and Biobehavioral Sci., UCLA, Los Angeles, CA; [5]Psychiatry, Washington Univ., ST. LOUIS, MO; [6]Anesthesiol., UCLA, Los Angeles, CA

Abstract: Dissecting the accumbal dynorphinergic outputs underlying affective pain
Flora D'Oliveira Da Silva, Hye Jean Yoon, Rossana Sandoval, Catherine Cahill, Marco Pignatelli, Jose Moron-Concepcion, Nicolas Massaly
Pain represents a growing epidemic in the U.S., afflicting more than 30% of the population. Despite the availability of effective treatments for acute nociceptive pain conditions, negative affective states induced by persistent or chronic pain remain under- or untreated. The nucleus accumbens (NAc) is a critical component of the mesolimbic system and is involved in integrating both reinforcing and aversive properties of external stimuli. Activation of kappa opioid receptors (KORs) through exogenous or endogenous agonist, dynorphin, produces dysphoric effects and impairs active coping strategies in preclinical models of pain. Using chemogenetic approaches and microPET imaging, we recently demonstrated that 1) dynorphin-containing (Dyn+) neurons in the NAc are necessary to drive pain-induced negative affect and 2) inflammatory pain increases overall central KORs occupancy. However, the nature of the downstream structures through which Dyn+ neurons mediate behavioral adaptations to pain

remain to be determined. Indeed, NAc Dyn+ neurons project to many structures involved in motivation including the Ventral Pallidum, the Ventral Tegmental Area (VTA) and the Lateral Hypothalamus (LH). Recent evidence has uncovered that Dyn+ neurons projecting from the Nac to the LH ($Dyn^{NAc->LH}$) are necessary to drive stress-induced anhedonia. In this line of thoughts, using both males and females adult mice we employed a combination of ex vivo physiology, imaging and behavioral pharmacology and determined that pain 1) increases the excitability of $Dyn^{NAc->LH}$ projections, 2) increases KOR function in the LH and 3) engages LH KOR signaling to decrease reward-driven motivation (n=8, $p<0.0001$). Our results participate in further understanding the allostatic changes in Dyn+ NAc synaptic efferents in pain and their impact on negative affective states.
Support: McDonnell Foundation Small Grant (NM), R21DA055047 (NM)
Conflict of Interest statement: The authors declare no conflict of interest.

Disclosures: F. D'Oliveira da Silva: None. **H. Yoon:** None. **R. Sandoval:** None. **C.M. Cahill:** None. **M. Pignatelli:** None. **N. Massaly:** None.

Poster

PSTR038: Processing Threats and Pain

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Program #/Poster #: PSTR038.17/L9

Topic: F.03. Stress and the Brain

Support: MH002386
AT000029

Title: Pacap in parabrachial nucleus projection to extended amygdala is required for pain sensitization in mice

Authors: S. SINGH[1], S. Z. JIANG[2], W. FORTUN[3], *L. E. EIDEN[4], Y. CARRASQUILLO[5]; [1]Natl. Ctr. for Complimentary and Integrative Hlth., Natl. Inst. of Hlth., Bethesda, MD; [2]Section on Mol. Neurosci., NIMH/NIH, Bethesda, MD; [3]Section on Behavioral Neurocircuitry and Cell. Plasticity, NCCIH, Bethesda, MD; [4]Section on Mol. Neuroscience, Lab. of Cell. and Mol. Regulation, NIMH-Intramural Res. Program, BETHESDA, MD; [5]Natl. Ctr. for Complementary and Integrative Hlth., NIH, Bethesda, MD

Abstract: Pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide found along the pain neuraxis, including in sensory neurons in the dorsal root ganglia, second-order neurons in the dorsal horn of the spinal cord, and third-order neurons in the parabrachial nucleus (PBn) that in turn project to extended amygdala (central amygdala, and oval portion of bed nucleus of the stria terminals (ovBNST). The PBn to extended amygdala pathway contributes to allodynia as well as aversive responses to threat, footshock and bitter tastants. We have previously shown that PACAP in the parabrachioamygdalar pathway make connections with PKCdelta neurons in central amygdala, and that deletion of PACAP from this pathway causes

interruption of signaling responsible for hypophagia after restraint stress (Jiang et al., Biol. Psychiatr. GOS 3: 673, 2023). Accordingly, we asked whether PACAP in this pathway might be required for pain sensitization after nerve injury or peripheral inflammation. Mice with constitutive deletion of PACAP were compared to wild-type mice in development of hypersensitivity (pain sensitization) following unilateral sciatic nerve cuffing, a model of neuropathic pain. Mice of either genetic background showed similar baseline responses to heat, cold, tactile, and pinch stimulation of the hindpaw using the Hargreaves, Acetone, von Frey, and Randall-Selitto tests, respectively. However, hypersensitivity to all stimuli, induced by unilateral sciatic nerve cuffing, failed to develop in PACAP knock-out mice compared to wild-type mice. Parallel experiments using the formalin model of inflammatory pain showed that phase 1 responses to formalin injection in the hindpaw were similar in the two groups, while phase 2 responses were delayed and reduced in PACAP knockout mice. Deletion of PACAP exclusively within the parabrachial projection to extended amygdala contralateral to sciatic nerve cuffing gave results similar to those obtained in PACAP knock-out mice: there was undiminished baseline responses to noxious stimuli, but dramatically reduced development of injury-induced hypersensitivity (i.e. augmented responses to heat, cold, tactile, and pinch stimuli). The PBn to extended amygdala is a major projection contributing to development of hypersensitivity after injury, and containing multiple transmitters including glutamate, acetylcholine, CGRP and PACAP. Our experiments show that the presence of one of these transmitters, the neuropeptide PACAP, is required for the synaptic transmission of sensory information leading to heightened responses to noxious stimuli after an injury.

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Poster

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Topic: F.03. Stress and the Brain

Support: Ed3C doctoral fellowship
European Research Council
Fondation Bettencourt Schueller

Title: Noradrenaline-mediated glial calcium wave: a physiological fuse evoking motor arrest

Authors: *M. DHANASEKAR[1,2], E. LUNSFORD[3], L. MOISAN[4], M. CARBO TANO[3], C. WYART[3];
[1]Paris Brain Inst., PARIS 13, France; [2]Sorbonne Université, Paris Brain Institute (Institut du Cerveau, ICM), Inserm U1127, CNRS UMR 7225, Paris, France; [3]Sorbonne Univ., Paris Brain Inst. (Institut du Cerveau, ICM), Inserm U1127, CNRS UMR 7225, Paris, France; [4]Applied Mathematics, Univ. Paris Cité, CNRS, MAP5, Paris, France

Abstract: Evading threats necessitates the deployment of complex avoidance strategies, such as the decision between escape and motor arrest. While the escape circuitry has been well characterized across species, the underlying mechanisms eliciting motor arrest remain elusive. Recent study in larval zebrafish demonstrated that upon sensory-motor mismatch, passivity involves noradrenergic signaling eliciting a brain-wide glial calcium wave. However, it remains unknown how noradrenergic activation translates into subsequent glial calcium waves and provokes motor arrest. The working hypothesis is that noradrenergic neurons integrate intensive sensory stimulations and control the decision and duration of motor arrest. Exploiting the transparency and genetic accessibility of larval zebrafish, we found that upon graded optogenetic activation of noradrenergic neurons, short activation (<1s) did not induce motor arrest, while long durations (>1s) induced prolonged motor arrest whose durations scaled with the duration of noradrenergic activation. These results suggest that sustained activation of noradrenergic neurons is required for the animal to employ motor arrest. To decipher the nature of the glial calcium wave associated with motor arrest, the activity of glial cells was monitored upon activating noradrenergic neurons. Short activations elicited a synchronous, small calcium rise confined to glia in the spinal cord, while long activations elicited a large glial wave that started in the rostral spinal cord and propagated to the brainstem, invading the obex, pons, and medulla. These findings indicate that sustained noradrenergic activation is necessary to induce a glial calcium wave that reaches the brainstem to elicit motor arrest. To dissect if the motor arrest was elicited due to synchronous bilateral activation of motor circuits vs the blockade of motor output, we employed extracellular recordings of motor neurons in paralyzed larvae with optogenetic activation of noradrenergic neurons. We found that optogenetic activation of noradrenergic neurons resulted in the inhibition of motor output concurrently with the propagating glial wave. Our work opens on the involvement of complex neuro-glial interactions in generating adaptive behavioral responses during threat perception.

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Poster

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Topic: G.04. Emotion

Support: P30GM145497
P20GM103643

Title: Neonatal pain alters the excitability of neurons expressing corticotropin releasing factor (CRF) in the central nucleus of the amygdala.

Authors: *M. E. TOMASCH[1,2], L. F. QUEME[3], M. A. BURMAN[3,4];
[1]Univ. of Maine Grad. Sch. of Biomed. Sci., Orono, ME; [2]University of New England,

Biddeford, ME; [3]Univ. of New England, Biddeford, ME; [4]University of Maine Graduate School of Biomedical Sciences, Orono, ME

Abstract: Stressful, traumatic, and/or painful events early in life have been shown to alter developmental trajectory, both physically and psychologically, and result in a vulnerability to pain- and anxiety disorders later in life. This effect is often observed in adolescents who had previously spent time in the neonatal intensive care unit (NICU) and has been successfully replicated in animal models. Using a rodent model of a typical NICU experience, our lab has observed an altered response to a subsequent stressor (e.g. fear conditioning) in rats that experienced neonatal trauma, with them presenting increased anxiety-like behaviors and increased sensitivity to mechanical stimulation following a second stressor (e.g., fear conditioning) at PD 24, an age considered “adolescence” for rats. Previously, we associated these behavioral changes in males with changes to cells expressing corticotropin-releasing factor (CRF) in the central nucleus of the amygdala (CeA)—with neonatal pain resulting in a reduction of CeA-CRF expression at PD 24, the time of the second stress event. Despite the reduced expression of CeA-CRF at the time of this second, activating stressor, literature suggests that these CeA-CRF+ neurons may be hyperactive. We hypothesize that neonatal trauma alters the response patterns of neurons within the CeA-CRF system, creating a pain-induced neural plasticity that primes for altered responses to future stressors as well as increased pain sensitivity later in life. To replicate a common NICU experience, neonatal rats receive a small needle prick in the hind paw four times a day, every two hours, for the first week of life. On PD 23-27, we performed acute-slice patch-clamp electrophysiology in transgenic rats expressing TdTomato in CRF+ neurons to assess the impact of neonatal trauma on CeA-CRF+ cell excitability. Whole-cell current-clamp recordings taken from transgenic rats expressing TdTomato in CRF+ neurons revealed that these cells display multiple distinct firing patterns, the distribution of which was altered by neonatal trauma. Our data show increased excitability of CeA-CRF+ cells following neonatal trauma, evidenced by an increased number of action potentials fired in response to current injections. Interestingly, neonatal pain also appears to create a resilience to depolarization blockade, allowing CeA-CRF+ neurons to maintain firing at higher current stimulations. Furthermore, our data suggest that neonatal trauma may result in a hyperpolarized resting membrane potential, as well as a reduced rheobase. These changes may account for later-life changes in affective, as well as pain-related behaviors.

Disclosures: **M.E. Tomasch:** None. **L.F. Queme:** None. **M.A. Burman:** None.

Poster

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Topic: G.04. Emotion

Support: P30GM145497
P20GM103643

University of New England, Office of Research and Scholarship
Kahn Family Foundation

Title: Nicu-like exposure induces a susceptibility to truama-induced tactile hypersensitivity mediated by neurons in the amygdala

Authors: *M. BURMAN, E. NAESS, B. WESLER, A. FOX;
Univ. of New England, Biddeford, ME

Abstract: Infants that spend time in the neonatal intensive care unit (NICU) face an elevated risk of developing adverse mental health outcomes and altered pain thresholds later in life. While the number of infants that spend time in the NICU has increased sharply in the past decade, our understanding of the neurobiological mechanisms that predispose this patient group to altered pain thresholds remains limited. We have adopted a rodent model that mimics the NICU experience to provide better insight into this phenomenon. Male Sprague Dawley rodents were subjected to hind paw needle pricks four times per day for the first week of life followed by fear conditioning on postnatal day (PD) 24. This is followed by an assessment of fear behavior in early adolescence on PD 25 and PD26 and an assessment of the tactile withdrawal threshold using Von Frey filaments on PD 27. We have previously established that this NICU-like experience, when followed by fear conditioning, induces a tactile allodynia that requires both stressors. In this study, we test the hypothesis that neurons in the amygdala are essential for the development of conditioning-induced hypersensitivity to tactile pain following NICU-like medical trauma. Following painful neonatal manipulations, neurons in the amygdala of male rats were silenced using a chemogenetic designer receptor exclusively activated by designer drugs (DREADD) approach during fear conditioning. For experiment 1: pAAV-hSyn-hM4D(Gi)-mCherry was targeted at the CeA, but spread to surrounding regions. Thus, chemogenetic silencing occurred of all neurons in the amygdala during fear conditioning. This greatly reversed the fear conditioning-induced hypersensitivity to tactile pain observed following early-life trauma. Experiment 2 targeted neurons in the central nucleus of the amygdala that express the neuropeptide corticotrophin-releasing factor using a combination of transgenic CRF-CRE rats and a cre-dependant pAAV-hSyn-DIO-hM4D(Gi)-mCherry. Silencing CRF-cells had a modest effect on the observed hypersensitivity. These findings suggest that activation of the amygdala is essential for a trauma-induced tactile hypersensitivity following early life NICU exposure.

Disclosures: **M. Burman:** None. **E. Naess:** None. **B. Wesler:** None. **A. Fox:** None.

Poster

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Topic: G.04. Emotion

Support: P30GM145497
P20GM103643
Kahn Family Foundation Summer Research Fellowship

Title: Impacts of nicu-like experience on cell population phenotype in the amygdala and hypothalamus

Authors: *B. M. MERRILL[1], M. E. TOMASCH[2,3], M. A. BURMAN[1];
[1]Univ. of New England, Biddeford, ME; [2]Univ. of Maine Grad. Sch. of Biomed. Sci., Orono, ME; [3]University of New England, Biddeford, ME

Abstract: Infants who spend time in the neonatal intensive care unit (NICU) demonstrate increased susceptibility to chronic pain and anxiety disorders later in life. Using a rodent model of a NICU-like experience, our lab has observed enhanced expression of corticotropin releasing hormone (*crh*) acutely following pain, with significant long-term reductions in *crh* expression in the right hemisphere of the central amygdala (CeA) of adolescent male rats. The CeA contains a heterogeneous population of cells - characterized by expression of various biomarkers (e.g., *crh*, prodynorphin [*pdyn*], somatostatin [*sst*], protein kinase C delta [*PKC-δ*]) - that have distinct functions in pain, fear, and anxiety. These biomarkers are well characterized in adults, with *crh*+ cells also co-expressing other pro- or anti-pain biomarkers like *pdyn* or *sst*. Thus, this project is innovative in examining how biomarker expression changes across development and in response to pain. We hypothesized that early life pain will alter the composition of biomarker-identifiable subpopulations (e.g., *crh*, *pdyn*, *sst*) within the CeA, basolateral amygdala (BLA), and hypothalamus, via a trauma-induced neural plasticity that primes for altered pain responses and anxiety-like behaviors in later life. Inspired by the heel lance blood draw on human infants, rats in our NICU-like environment experienced hindpaw pricks four times a day - every two hours - for the first week of life. On post-natal day (PD) 12, 24, and 48, brain tissue was collected from male and female rats that experienced neonatal pain or were left undisturbed (n=5 per group). Changes in cellular phenotype of the CeA, BLA, and hypothalamus were assessed across development, using RNAscope fluorescent *in situ* hybridization (fISH) to visualize and quantify (co-) expression of *crh*, *pdyn*, and *sst*. Among our twelve experimental groups that account for behavioral manipulation (undisturbed/control or NICU), sex (male or female), and age (neonate = PD 12, juvenile = PD 24, or adolescent = PD 48), we find age-dependent changes in the quantity, co-expressing biomarker-phenotype, and overall developmental trajectory of male *crh*+ cells, with a large change in *crh* expression following the NICU-like exposure and a subsequent decline in *crh* expression in the NICU-exposed subjects. Female subjects showed developmental changes, but no statistical effect of the NICU manipulation. Therefore, data suggest that NICU-like experiences may lead to changes in male developmental trajectory of *crh* expression in the CeA and altered specialization of these cells, which may account for changes in emotional and pain behaviors later in life.

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Poster

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Mobility Grant 1662/1/MOB/V/17/2018/0

Title: Investigation of the anterior cingulate cortex neural circuits regulating pain behaviors

Authors: *S. MATOS[1], D. PETERS[1], K. M. TARGOWSKA-DUDA[2], A. MUDGAL[2], K. HARBIN[1], L. TOLL[1,3], A. OZAWA[1,3];
[1]Florida Atlantic Univ., Boca Raton, FL; [2]Med. Univ. of Lublin, Lublin, Poland; [3]Stiles-Nicholson Brain Institute, Jupiter, FL

Abstract: Chronic pain presents a significant clinical challenge, often leading to debilitating physical and emotional distress. The anterior cingulate cortex (ACC) is a key brain region implicated in chronic pain and its associated emotional responses. However, there is a lack of comprehensive understanding of the mechanism by which specific neural circuitry involved in the development of pain and emotional changes associated with chronic pain conditions, and how medications function to alleviate pain by acting on specific neuronal circuits. Here, we investigate the role of ACC neurons in regulating pain behaviors and the brain regions that regulate ACC circuits during chronic pain, using TRAP2 (Fos2A-iCreERT2) mice, which allow us to target neurons active during chronic pain, combined with chemogenetics and rabies virus-based monosynaptic neural tracing. Chemogenetic neuronal manipulation demonstrates that inactivating ACC neurons active during chronic pain attenuates sensory pain and produces conditioned place preference (CPP) in SNL mice compared to controls. These data suggest that ACC neurons active during chronic pain are important in regulating both sensory and affective components of pain. We also find a sexual dimorphism: CPP is only induced in male SNL mice, while chronic pain-induced anxiety is only reduced in female SNL mice when the activity of ACC neurons active during chronic pain is chemogenetically inhibited. Interestingly, similar sexual dimorphisms in regulating pain behaviors are also observed when gabapentin was administered to SNL mice. In rabies virus-based monosynaptic tracing, we identify input cells in the brain regions important for regulating pain-related behaviors, suggesting that these brain regions potentially regulate the ACC neuronal activity during chronic pain. The results provide both anatomical and functional evidence that the ACC circuitry is essential in regulating the behaviors associated with chronic pain and will provide us with further insight into the function of ACC circuits in pain modulation.

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Poster

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Topic: F.03. Stress and the Brain

Support: FAPESP (grant # 2022/06260-3)
FAPESP (grant # 2020/11827-7)

Title: Corticotropin releasing factor (CRF) control of neuronal activation in the medial prefrontal cortex during retrieval of contextual fear conditioning is lateralized and receptor subtype specific

Authors: *L. GOMES-DE-SOUZA[1], A. SANTOS[1], C. BUSNARDO[2], C. S. PLANETA[1], R. L. NUNES-DE-SOUZA[3], C. CRESTANI[4];
[1]São Paulo State Univ., Araraquara, Brazil; [2]Sao Paulo State Univ., Ribeirão Preto, Brazil; [3]Pharmacol., Sao Paulo State Univ., Araraquara, Brazil; [4]Univ. of Cincinnati, Cincinnati, OH

Abstract: INTRODUCTION: (mPFC) is involved in the expression of conditioned responses. A functional lateralization was described in the control by the mPFC of responses to aversive stimuli. in this sense, previous studies indicated that the right mPFC, while the left mPFC would have a counter-regulatory role by inhibiting the right mPFC. Additionally, local (CRF) neurotransmission has been reported as an important local neurochemical mechanism involved in mPFC control of stress responses. Despite these pieces of evidence, a role of local CRF neurotransmission in lateralized control of conditioned responses by the mPFC has never been documented. **OBJECTIVE:** To investigate the role of local CRF neurotransmission in local neuronal activation within the mPFC in animals submitted to contextual fear conditioning, and whether this control is lateralized. **METHODS:** Male Wistar rats had cannula-guide implanted either bilaterally or into the right or left hemispheres of the mPFC. For the conditioning, each animal was placed individually in the conditioning chamber and received six shocks (1,5mA/3s). Twenty-four hours after the conditioning session, the animals were submitted to femoral artery cannulation surgery for cardiovascular recording. The fear retrieval test was performed 48 hours after the conditioning session. Independent set of animals received microinjections into either the left, right or both hemispheres (bilateral) of the mPFC of vehicle (saline, 100nL), the selective CRF_1 receptor antagonist CP356395 (5nmol/100nL) or the selective CRF_2 receptor antagonist antisalvagine-30 (5nmol/100nL) 10 min before the fear retrieval test. Eighty minutes after the end of the test session, the animals were anesthetized with urethane and perfused for posterior immunohistochemistry assay for staining Fos protein. **RESULTS:** Bilateral microinjection of either CP376395 or antisalvagine-30 into the mPFC did not affect the local number of Fos-positive cells (P=0,8431). Nevertheless, antagonism of CRF_2 receptors within the right hemisphere of the mPFC increased the number of Fos-positive cells ipsilaterally (P=0,0023), but without affecting neural activation contralaterally (P0,05). Treatment of the left mPFC with either CP376395 or antisalvagine-30 also increased the number of Fos-positive cells ipsilaterally (CP376395: P=0,0267; antisalvagine-30: P=0,0002), but not contralaterally (P0,05). **CONCLUSIONS:** These results indicate an inhibitory influence of CRFergic receptors in local neuronal activation within the mPFC during retrieval of contextual fear conditioning, and this control seems to be receptor subtype-and hemisphere-dependent.

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Poster

PSTR038: Processing Threats and Pain

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Topic: G.04. Emotion

Title: Neuropeptide Y (NPY) release into the medial prefrontal cortex (mPFC) inhibits local parvalbumin neurons, a possible mechanism for anxiolysis

Authors: *E. DIMITROV;
RFUMS, North Chicago, IL

Abstract: Neuropeptide Y (NPY) is a neurotransmitter and neuromodulator found throughout the CNS. The NPY modalities a myriad of homeostatic behaviors, including feeding, anxiety, and pain. The anxiolytic functions of NPY are attributed to the activation of the Y1 receptor (Y1r). NPY cells populate all layers of the medial prefrontal cortex (mPFC), but the downstream targets of cortical NPY transmission remain underexplored. We conducted a series of experiments that show that the NPY release in the mPFC inhibits the local parvalbumin neurons (PV). We use a combination of behavior tests for mice, neuronal tracing, fiber-photometry, and ICV injections to document the effects of NPY signaling on mice's behavior and related neuronal activity. First, the mice received bilateral injections of either vehicle or the Y1r antagonist BIBO3304 in the mPFC and tested on the elevated O-maze (EOM) for anxiety-like behaviors. Administration of 100 nmol BIBO3304 significantly decreased the time spent in open compartments of the maze (T-test, $df_{18} = 2.3$, $P < 0.05$), therefore confirming NPY anxiolytic actions executed via Y1r. To determine the downstream targets of NPY neurons, an anterograde tracer (AAV1.Syn.FLEX.tdTom.T2A.SypEGFP), which labels presynaptic boutons, was injected into the mPFC of NPY-cre mice. Three weeks later, brain sections from the injected mice were immunostained for PV interneurons. The analysis of the colocalization between the PV and the Synapsin (GFP) voxels demonstrated close proximity between the two markers, which indicates that PV interneurons are targeted by NPY axons. To further confirm that the PV interneurons are downstream target of NPY signaling, a group of mice were injected into the mPFC with pAAV9-S5E2-GCaMP6f, where the GCaMP6 expression is restricted to the PV cells. The mice received an optic fiber with a cannula attached to it, hence allowing fiberphotometry recordings during EOM test after intracerebral injections into the recording site. Injection of 10 pmol NPY reduced the activity of the PV interneurons in mice exploring the maze, as reflected by the lower fluorescent signal generated by the cortical PV interneurons (AUC, paired T-test, $t_6 = 5.3$, $P < 0.01$). The fluorescent intensity of the GCaMP corresponds to the populational activity of the labeled neurons; therefore, the result supports our hypothesis that the release of NPY into the mPFC inhibits the activity of the local PV neurons. In conclusion, our results show that NPY

signaling in the mPFC is an important behavioral modulator and that NPY-induced anxiolysis is very likely a result of inhibition of the cortical PV interneurons.

Disclosures: E. Dimitrov: None.

Poster

PSTR038: Processing Threats and Pain

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.25/L17

Topic: F.03. Stress and the Brain

Support: R01 HL150559

Title: Infralimbic prefrontal cortical projections to the brainstem: inputs to acetylcholine- and epinephrine/norepinephrine-producing nuclei

Authors: *E. LUKINIC[1], T. WALLACE[2], C. MCCARTNEY[3], B. MYERS[3];
[1]Biomed. Sci., Colorado State Univ., Timnath, CO; [2]Colorado State Univ., Fort Collins, CO; [3]Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: The ventromedial prefrontal cortex regulates both emotional and physiological processes. In particular, the infralimbic cortex (IL) integrates behavioral, neuroendocrine, and autonomic responses to stress. However, the organization of cortical inputs to brainstem nuclei that regulate homeostatic responses are not well defined. Therefore, we hypothesized that IL projections differentially target pre-ganglionic parasympathetic neurons and adrenergic/noradrenergic nuclei. To quantify IL projections to autonomic brainstem nuclei in male rats, we utilized viral-mediated gene transfer to express yellow fluorescent protein (YFP) in IL glutamatergic neurons. YFP-positive projections to cholinergic and adrenergic/noradrenergic nuclei were then imaged and quantified. Cholinergic neurons were visualized by immunohistochemistry for choline acetyltransferase (ChAT), the enzyme responsible for the synthesis of acetylcholine. Adrenergic/noradrenergic neurons were visualized with immunohistochemistry for dopamine beta hydroxylase (DBH). DBH converts dopamine to norepinephrine, which also serves as a precursor for epinephrine. Our results indicated that IL glutamate neurons innervated the cholinergic dorsal motor nucleus of the vagus with greater density than the nucleus ambiguus. Furthermore, numerous DBH-positive cell groups received IL inputs. The greatest density was to the C2 and A2 regions of the nucleus of the solitary tract with intermediate levels of input to A6 locus coeruleus and throughout the C1 and A1 regions of the ventrolateral medulla. Minimal input was present in the pontine A5. Additionally, we found that these cortical synapses also targeted local GABA neurons that regulate the identified excitatory neurons, suggesting potential bidirectional control. Collectively, our results indicate that IL projection neurons target vagal preganglionic parasympathetic neurons, presympathetic neurons of the ventrolateral medulla, as well as diffuse modulators of homeostatic function that arise from the nucleus of the solitary tract and locus coeruleus. Ultimately, these findings provide

a roadmap for determining circuit-level mechanisms for neural control of homeostasis and autonomic balance.

Disclosures: **E. Lukinic:** None. **T. Wallace:** None. **C. McCartney:** None. **B. Myers:** None.

Poster

PSTR038: Processing Threats and Pain

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Program #/Poster #: PSTR038.26/L18

Topic: F.03. Stress and the Brain

Support: NIH Grant 1R01HL173525
NIH Grant 1F32HL172693

Title: Synaptic and neurochemical properties of the infralimbic-posterior hypothalamic circuit

Authors: *C. A. BOUCHET, J. R. BROWN, S. A. PACE, C. E. VAAGA, B. MYERS;
Dept. of Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: Cardiovascular diseases, the leading cause of death globally, are exacerbated by psychosocial stressors including mood and anxiety disorders. Additionally, mood-cardiovascular comorbidities are more prevalent in females. However, the neurobiological mechanisms underlying the relationships between behavior and physiology have only recently been studied in a sex-specific manner, as prior research has predominantly investigated male physiology and neurobiology. Therefore, this project investigates neurobiological mechanisms underlying sexually-divergent stress regulation. Recent work identified that the neural projection from the infralimbic region of the prefrontal cortex (IL) to the posterior hypothalamus (PH) regulates motivated behavior and physiological stress responses in a sexually-divergent manner. The current study tests the hypothesis that sex-specific synaptic signaling and transcriptional responses account for sexual divergence in circuit function. Adult male and female rats (PND 72-141) were used for whole-cell recordings and transcriptional analyses. Optogenetic slice electrophysiology experiments indicated that the projection neurons from the IL to PH were predominantly glutamatergic, as optically-evoked currents were blocked by ionotropic glutamate receptor antagonists. IL projection neurons synapsed onto both GABAergic and glutamatergic PH neurons, as assessed by viral-mediated anterograde tracing combined with immunohistochemistry and RNAscope. To determine the neurophysiology of cells within the PH, patch clamp electrophysiology was used to investigate spontaneous firing properties of PH neurons in unstressed rats. Data indicate that PH neurons predominantly fire at rest, with the minority of neurons silent at rest in both males and females. While many properties of spontaneous firing were similar between males and females, female PH neurons were more excitable upon current injection. Transcriptional data from PH homogenates indicated that male and female neurons also respond differentially to chronic variable stress. Accordingly, ongoing experiments aim to understand these transcriptional changes both spatially and functionally.

Altogether, these experiments dissect this cortical-hypothalamic neural pathway from the level of transcription to function and highlight neural mechanisms that could underly the sex bias in comorbidities between mood disorders and cardiovascular disease.

Disclosures: **C.A. Bouchet:** None. **J.R. Brown:** None. **S.A. Pace:** None. **C.E. Vaaga:** None. **B. Myers:** None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.01/L19

Topic: G.09. Drugs of Abuse and Addiction

Support: NCBC (Translational Research Grant AWD-20-1435-002)

Title: The dopamine D3 receptor agonist pramipexole decreases withdrawal in morphine tolerant rats

Authors: A. DAVIS[1], D. MARSHALL[2], S. CLEMENS[3], ***K. BREWER**[4];
[1]Brody Sch. of Med. @ East Carolina Univ., Greenville, NC; [2]Brody Sch. of Med., Greenville, NC; [3]Physiol., Brody Sch. of Med. @ East Carolina Univ., Greenville, NC; [4]East Carolina Univ., Greenville, NC

Abstract: Despite their dangerous side effects, opioid drugs remain a standard of care for moderate to severe pain with few alternatives. Strategies to maintain the analgesic effects of opioids while minimizing the risk for tolerance, dependance and withdrawal are needed. We previously demonstrated that a combination of morphine and pramipexole (PPX) restored analgesia in morphine-tolerant animals. The aim of this study was to assess if this same combination of morphine/PPX could attenuate opioid withdrawal symptoms in opioid tolerant animals.We induced tolerance in 18 male Long-Evans rats with a twice daily subcutaneous injection of 10 mg/kg morphine for 7 days. At 7 days, drug administration was either stopped (control group, n=6), or animals were assigned to one of two drug conditions for the next 7 days: 5 mg/kg dose of morphine (n=6, MOR group) or a 5 mg/kg dose of morphine plus 0.5 mg/kg pramipexole (n=6, MOR/PPX group). Withdrawal symptoms were assessed at the start of treatment and after all drug administration was stopped. The control group displayed multiple behaviors associated with withdrawal when drug delivery was stopped. Animals in the MOR treatment group showed overall similar withdrawal behaviors as the control group during treatment, while animals in the MOR/PPX group displayed a reduction in 8 of the 14 withdrawal behaviors probed (weight, irritability, scratching, genital licking, wiping, chattering, grooming, and chewing). Animals in the MOR/PPX group also displayed significantly more jumping and rearing behaviors than the other groups. After controlling for rearing behaviors, which are specifically associated with the use of dopaminergic drugs, there was a significant reduction in withdrawal symptoms in the MOR/PPX treatment group when compared to control at both 48

(p=0.014) and 72 hours (p=0.004). Our data show that treatment with a lowered dose of morphine in combination with PPX decreased withdrawal symptoms seen in morphine tolerant rats. This provides preclinical evidence that the D3 receptor system may be an appropriate tool for developong a potential opioid replacement therapy. Future research will investigate if a stepwise decrease in doses of the morphine/PPX combination over time will also reduce withdrawal after complete removal of drug in morphine-tolerant animals.

Disclosures: A. Davis: None. **D. Marshall:** None. **S. Clemens:** 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.; Amalgent Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amalgent Therapeutics, Inc. **K. Brewer:** 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.; Amalgent Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amalgent Therapeutics, Inc..

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.02/L20

Topic: G.09. Drugs of Abuse and Addiction

Support: CIC-UMSNH 18096
CIC-UMSNH 18099
ICTI-PICIR23-058
CIC-UMSNH 18146

Title: Xylene and benzene exposure enhances acute and chronic formalin-induced nociception in rats

Authors: D. A. SIMON[1], L. F. ORTEGA-VARELA[2], D. GODINEZ HERNANDEZ[3], C. J. GUTIERREZ-GARCIA[4], *M. Y. GAUTHEREAU-TORRES[1];
[1]Facultad de Ciencias Medicas y Biologicas "Dr. Ignacio Chavez", [2]Facultad de Salud Publica y Enfermeria, [3]Inst. de Investigaciones Quimico Biologicas, Univ. Michoacana de San Nicolas de Hidalgo, Morelia, Mexico; [4]Ingenieria Quimica y Bioquimica, TecNM/Campus Morelia, Morelia, Mexico

Abstract: Xylene and benzene are misused inhalants that can alter the state of awareness, they are found in commercial products such as paint removers, paint thinner, gasoline and glue. Inhalant abuse is considered a public health problem, mainly among children and teenagers.

Studies have indicated that abused solvents share various mechanisms of action with central nervous system depressants, such as alcohol. In contrast, there is evidence indicating that exposure to toluene (an abused solvent with a chemical structure similar to xylene and benzene) has pronociceptive action and promotes hyperalgesia and allodynia. However, it is unknown the participation of other abused solvents in nociception or if other solvents share the effects of toluene. Therefore, the aim of this study was to assess the effect of xylene and benzene exposure on nociception, hyperalgesia and allodynia. Male and female Wistar rats were acutely exposed to xylene and benzene (6000 and 8000 ppm, respectively) or air. Acute nociception was assessed using the formalin test, rats were injected subcutaneously on the dorsum of the right hind paw with 50 µl of 1% formalin and were evaluated for 1 minute every 5 minutes for 1 hour. Secondary hyperalgesia and allodynia were evaluated 12 days later in the same animals using von Frey filaments. All data are the mean ± S.E.M. of 6 animals per group. Our results showed that acute exposure to xylene and benzene increased formalin-induced acute nociception and promotes hyperalgesia and allodynia. There were no significant sex differences in the data registered ($p > 0.05$). The area under the number of paw withdrawals against time curve (AUC) after xylene and benzene exposure was higher compared to air group + 1% formalin ($p < 0.05$) on acute and long lasting nociception. Our findings suggest that xylene and benzene have pronociceptive effects in a similar way to toluene. Studies are currently underway to establish if these inhalants share nociceptive mechanisms of action with toluene.

Disclosures: D.A. Simon: None. **L.F. Ortega-Varela:** None. **D. Godinez Hernandez:** None. **C.J. Gutierrez-Garcia:** None. **M.Y. Gauthereau-Torres:** None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.03/L21

Topic: G.09. Drugs of Abuse and Addiction

Support: CIC-UMSNH 18096
CIC-UMSNH 18146
CIC-UMSNH 18099
ICTI-PICIR23-058

Title: Chronic toluene exposure modifies cardiovascular adrenergic response in the anesthetized rat

Authors: M. Y. GAUTHEREAU-TORRES[1], L. QUIROZ GARCIA[1], L. F. ORTEGA-VARELA[2], *D. GODINEZ-HERNANDEZ[3];
[1]Facultad de Ciencias Medicas y Biologicas "Dr. Ignacio Chavez", Univ. Michoacana de San Nicolas de Hidalgo, Morelia, Mexico; [2]Facultad de Salud Publica y Enfermeria, Univ. Michoacana de San Nicolas de Hidalgo, Morelia, Mexico; [3]Inst. de Investigaciones Quimico Biologicas, Univ. Michoacana de San Nicolas de Hidalgo, Morelia, Mexico

Abstract: Inhalants are misused substances with a diverse nature that only share the route of administration. Toluene is an inhalant, which is a volatile solvent found in many household products that are legal, cheap and easy to acquire and are used recreationally to produce mind-altering effects. This solvent shares pharmacological properties with central nervous system depressants. In the cardiovascular system, toluene increases blood pressure, produces arrhythmias, tachycardia, and sensitization to catecholamines and finally death, but the mechanisms of action are unknown. The aim of this study was to investigate if chronic toluene exposure modifies the cardiovascular adrenergic response in the anesthetized rat. Male Wistar rats (300-400 g) were chronically exposed to toluene (6000 ppm) or to air (control). Exposures were performed in static exposure chambers for 30 minutes, twice a day, during 4 weeks. Once the animals were exposed, rats were anesthetized and dose-response curves to phenylephrine (an alpha-1 adrenergic agonist) were performed, in the absence and in the presence of BMY 7378 (an alpha-1D adrenergic antagonist). Our results showed that anesthetized rats that were exposed to toluene had a higher basal diastolic and systolic blood pressure compared with the air-exposed group. On the other hand, chronic toluene exposure produced a lower diastolic and systolic blood pressure compared with control group when dose-response curves to phenylephrine were made. In addition, in order to study the participation of alpha 1D-adrenergic receptors, dose-response curves in the presence and in the absence of BMY 7378 were constructed, and we observed that diastolic and systolic blood pressure were lower in toluene-exposed rats that received BMY-7378 compared with solvent-exposed rats without antagonist. This effect was also observed in the air-exposed group. In conclusion, our results suggest that toluene modifies vascular alpha-1-mediated adrenergic response.

Disclosures: M.Y. Gauthereau-Torres: None. **L. Quiroz Garcia:** None. **L.F. Ortega-Varela:** None. **D. Godinez-Hernandez:** None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.04/L22

Topic: G.09. Drugs of Abuse and Addiction

Support: DA045364
DA031725

Title: Effects of xylazine on naloxone-precipitated fentanyl withdrawal in male and female rats

Authors: *H. CARLSON;
Neuroscience, Psychology, Lake Forest Col., Lake Forest, IL

Abstract: Fentanyl-xylazine or “tranq-dope” was recently declared an emerging national health threat in light of rising xylazine-positive overdose deaths and increasing cases of xylazine-adulterated fentanyl supplies nationwide. Given the recency of this development, very little is

known about the behavioral pharmacology of fentanyl-xylazine combinations. Anecdotal reports suggest that xylazine may lengthen the duration of fentanyl's effects, worsen the withdrawal state, and produce distinct withdrawal symptoms, thereby requiring alternative clinical interventions than fentanyl alone. Male and female Long Evans rats were given twice daily (08:00 and 20:00) subcutaneous injections of fentanyl (0.1 mg/kg), xylazine (0.6 or 2.0 mg/kg), or combined fentanyl-xylazine for five days. On the sixth (testing) day, rats were given a final injection at 08:00. Exactly four hours later, rats were injected intraperitoneally with either a saline (1 ml/kg) or naloxone (10 mg/kg) challenge dose before behavioral observation. The effects of chronic xylazine treatment on the severity of naloxone-precipitated withdrawal were examined using the Gellert-Holtzman scale (GHS), which includes both graded and checked (present/absent) somatic markers of withdrawal and the elevated plus maze (EPM) to assess anxiety-like behavior. Naloxone administration did not result in significantly different scores on either the GHS or EPM in male or female rats receiving fentanyl or xylazine alone. However, naloxone produced a significant increase in somatic withdrawal signs on the GHS in male, but not female, rats, without impacting anxiety-like behavior on the EPM. Taken together, these data indicate that xylazine enhances the somatic symptoms of naloxone-induced fentanyl withdrawal in males. Overall, this pattern of results suggests that novel clinical interventions may be required to treat withdrawal from combined fentanyl-xylazine ("tranq-dope") in humans.

Disclosures: H. Carlson: None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.05/L23

Topic: G.09. Drugs of Abuse and Addiction

Support: IMSD T32 GM139807

Title: Differential Effects of Repeated Toluene Exposure on Locomotor and Neuronal activity in Female and Male Mice

Authors: *J. L. CARTHAGE[1], S. A. PERRINE[2], S. E. BOWEN[3];
[1]Wayne State Univ., Detroit, MI; [2]Psychiatry and Behavioral Neurosciences, Wayne State Univ., Detroit, MI; [3]Psychology, Wayne State Univ., Detroit, MI

Abstract: Inhalant abuse is a worldwide public health concern, particularly among adolescents. Recent research shows, that 2.3 million people aged 12 or older have used inhalants in the past year in the US. Limited studies have examined the behavioral effects of repeated toluene exposure in adolescence and even less including females. We aimed to address the gap in the literature by examining the dose-dependent effects of toluene inhalation between males and females, as well as the differential effects of acute and repeated toluene exposure on rodent behavior and neuronal activity. Adolescent male and female Swiss Webster mice (PN 27-38)

were exposed to toluene concentrations of 0, 2000, and 4000 parts per million (ppm) for either 30 minutes daily for 10 days or one 30 min session. Locomotor activity was observed during each session. After the session on day 10, animals were euthanized, and their brains were processed for Fos analysis via immunofluorescent microscopy. Acutely, toluene produced a concentration-dependent increase in locomotor activity. With repeated exposure, locomotor sensitization was observed with increased locomotor activity over 10 days at 4000 ppm that differed significantly from the controls. Additionally, the 4000 ppm concentration of toluene led to a significant greater locomotor activity for males as compared to female mice. Ongoing experiments are examining the effects of repeated exposure compared to acute exposure on FOS activation in male and female mice.

Disclosures: **J.L. Carthage:** None. **S.A. Perrine:** None. **S.E. Bowen:** None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.06/L24

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant UG3DA050271

Title: Methadone ameliorates the effects of morphine withdrawal in a modified rat model of physical dependence

Authors: ***S. CHEETHAM**[1], E. BILLINGHAM[1], M. BURNETT[1], S. DYKES[1], S. JACKSON[1], D. RIAL[1], C. SIMMONS[1], L. KIRKPATRICK[2], L. PESTANO[2];
[1]Sygnature Discovery, Nottingham, United Kingdom; [2]Ensysce Biosci. Inc, La Jolla, CA

Abstract: There are no reported animal models to assess novel treatments of opiate withdrawal associated with opioid use disorder (OUD). In this study, methadone, a synthetic opioid agonist used clinically for OUD, has been assessed in a modified rat model of physical dependence. Male Sprague-Dawley rats (n=30) were administered vehicle for 3 days and then randomized into 2 groups receiving vehicle (po bid; n=10) or morphine (30 mg/kg po bid, n=20) for 16 days. Morphine was stopped and rats given vehicle (n=9) or methadone (20 mg/kg po bid, n=9) for the next 7 days. Body weight, food and water intake and a wide range of behaviors (blinded) were assessed daily. As expected, morphine initially increased body weight on Day 2 followed by a decrease from Day 5 onwards. Food intake decreased on all days (1-14) and water intake increased on Day 1 and then decreased from Day 3 onwards. Morphine produced typical opioid use behaviors (e.g. hunched posture, Straub tail, increased body tone and locomotor activity). Upon stopping morphine and starting vehicle dosing, an initial decrease in body weight and food and water intake were observed followed by rebound hyperphagia and hyperdipsia. Clear evidence of withdrawal was observed by the addition of new behaviors and physical signs (e.g. arched back, high stepping, decreased body tone, tail rattle, piloerection and increased

respiration). Administering methadone or vehicle reduced body weight and food intake for the first few days after morphine withdrawal. However, the rebound hyperphagia and hyperdipsia observed on Days 19 -23 with vehicle were significantly blunted in the methadone group. Methadone also significantly attenuated some behaviors observed during morphine withdrawal in the vehicle group including arched back, high stepping, piloerection, decreased body tone and increased respiration. Physical signs observed during the withdrawal phase in the methadone group but not seen with vehicle included those typical of continued opioid use (e.g. Straub tail, ataxia/rolling gait, stereotypy, explosive movements, decreased respiration). Interestingly some of these signs only lasted for the first few days of methadone dosing (Days 17-20) before returning to levels observed in the vehicle group. In conclusion, the morphine withdrawal effects on food and water intake as well as some withdrawal behaviors are blunted by methadone use in this rat model. In addition, some behaviors associated with opioid use that decrease during morphine withdrawal continue during methadone dosing for several days. This model may be useful for assessing the effect of OUD therapeutics on withdrawal symptoms.

Disclosures: S. Cheetham: A. Employment/Salary (full or part-time):; Sygnature Discovery. **E. Billingham:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **M. Burnett:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **S. Dykes:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **S. Jackson:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **D. Rial:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **C. Simmons:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **L. Kirkpatrick:** A. Employment/Salary (full or part-time):; Ensysce Biosciences Inc. **L. Pestano:** A. Employment/Salary (full or part-time):; Ensysce Biosciences Inc.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.07/L25

Topic: G.09. Drugs of Abuse and Addiction

Support: NHMRC Ideas Grant 20222048

Title: Incubation of craving for alcohol-associated cues is reduced by voluntary wheel running

Authors: *C. J. PERRY[1], J. L. CORNISH[2], A. J. LAWRENCE[3];
[1]Macquarie Univ., Sydney, Australia; [2]Psychological Sci., Macquarie Univ., North Ryde, Australia; [3]Florey Inst. of Neurosci. & Mental Hlth., Parkville, Australia

Abstract: Incubation of craving is the time dependent increase in craving elicited by drug-associated cues. This is well documented in clinical populations, and can be modelled in rodents by measuring changes to cue-elicited drug-seeking. Surprisingly, although incubation of craving is evident in people seeking treatment for alcohol use disorder, there are few preclinical studies that report on the mechanism underlying this effect in the specific context of alcohol. We trained

rats to self-administer alcohol, and then kept them in abstinence for 28 days. Cue-induced alcohol seeking was tested on day 1 or day 29 of abstinence. In addition, half the rats had access to a running wheel across abstinence. Following test, all rats were perfused transcardially. Brains were collected, and brain-wide neural activity was estimated by quantifying expression of c-Fos protein using QUINT workflow. Cue-induced relapse was greater on day 29 compared to day 1, and this effect was attenuated in rats that had access to running wheels (Interaction: $F[2,15] = 12.18$, $p < .001$, follow up pairwise comparisons $p < .05$). In key reward-associated neural loci, including prefrontal cortex, nucleus accumbens, basolateral and central amygdala, c-Fos immunoreactivity was similarly higher in rats tested on day 29 compared to day 1, and again this was attenuated in the exercise group. These finding confirm that the potential for alcohol-associated cues to precipitate relapse increases across abstinence. Furthermore, they imply that neuroadaptations leading to this increase may be reversed by voluntary exercise, suggesting that exercise is a viable intervention for mitigating relapse risk.

Disclosures: C.J. Perry: None. **J.L. Cornish:** None. **A.J. Lawrence:** None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

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5R25GM061151-19

Title: Temperature and Ethanol Dose-Dependent Regulation of Hemocyte-Mediated Ethanol Sensitivity

Authors: *M. KUCHIBHOTLA[1], A. MONTES-MERCADO[2], J. RODRIGUEZ CORDERO[3], J. MARRERO[4], C. MALDONADO-VALEDON[5], J. L. AGOSTO[6], A. GHEZZI[7], T. GIRAY[8], M.-E. PEREZ-HERNANDEZ[9];
[1]Biol., Univ. of Puerto Rico, San Juan, PR; [2]Dept. of Biol., Univ. of Puerto Rico- Rio Piedras, SAN JUAN, PR; [3]Univ. of Puerto Rico, Rio Piedras, Rio Piedras, PR; [4]Biol., UPR - Rio Piedras, San Juan, PR; [5]Biol., Univ. de Puerto Rico, Rio Piedras, San Juan, PR; [6]Biol., Univ. of Puerto Rico, Rio Piedras Campus, San Juan, PR; [7]Dept. of Biol., Univ. of Puerto Rico, Rio Piedras, San Juan, PR; [8]Dept. of Biol., Univ. of Puerto Rico, Rio Piedras, PR; [9]Mathematics, Univ. of Puerto Rico, Rio Piedras, PR

Abstract: Alcoholism ranks as the third leading cause of mortality worldwide. A critical factor in its development is the progressive increase in alcohol tolerance following repeated exposures. This phenomenon is mediated by neural adaptations and plasticity within the brain, ultimately leading to Alcohol Use Disorder (AUD). Recent research has shed light on the crucial role of the neuroimmune system in AUD development. Well-established studies have demonstrated a correlation between polymorphisms in macrophage and immune genes with a heightened risk of alcoholism, highlighting the significance of immune function and neuroimmune signaling in alcohol dependence. In the fruit fly, the RNA-binding protein pumilio (pum) has been identified as a regulator of ethanol tolerance. Notably, pumilio is also implicated in innate immune function, suggesting a potential convergence between these processes. This research aims to address the current knowledge gap by investigating the interactive effects of temperature and ethanol dosage on alcohol tolerance. To investigate the interplay between temperature, ethanol dosage, and pumilio expression on ethanol sensitivity, we employed the GAL4/UAS binary expression system. This system allowed for targeted expression of green fluorescent protein (GFP) or pumilio RNA interference (pumRNAi) transgenes specifically within hemocytes. A two-day ethanol assay paradigm was employed to assess sensitivity. In which, age-matched F1 female Drosophila flies were used. To elucidate the interaction between temperature and ethanol dose,flies were exposed to three different temperatures on separate occasions. At each temperature, flies were exposed to three different ethanol concentrations simultaneously.. Within the same genotype, sensitivity increased with higher temperatures. Additionally, pumilio knockdown further amplified this temperature-dependent sensitivity. An increasing ethanol dosage consistently elevated sensitivity irrespective of temperature. However, the rate of this increase, as indicated by the slope of the dose-sensitivity curve, was significantly steeper at higher temperatures. This suggests a potentiating effect of temperature on ethanol sensitivity. Importantly, at all tested temperatures, sedation levels appeared to reach a saturation point at higher ethanol concentrations. These results suggest that the mechanisms underlying ethanol tolerance are more complex than simply increasing the dose. The interaction between temperature and dose appears to play a crucial role. These findings highlight the importance of environmental factors, such as temperature, in ethanol sensitivity.

Disclosures: **M. Kuchibhotla:** None. **A. Montes-Mercado:** None. **J. Rodriguez Cordero:** None. **J. Marrero:** None. **C. Maldonado-Valedon:** None. **J.L. Agosto:** None. **A. Ghezzi:** None. **T. Giray:** None. **M. Perez-Hernandez:** None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.09/L27

Topic: G.09. Drugs of Abuse and Addiction

Title: Developing an ontology for quantifying risk of transitioning from occasional opioid use to opioid use disorder

Authors: *A. SECMEN[1], S. HARLEY[2], P. W. GLIMCHER[3];
[1]NYU Grossman Sch. of Med. Neurosci. Inst., New York, NY; [2]New York Univ., New York City, NY; [3]Neurosci. Inst., NYU Grossman Sch. of Med., New York, NY

Abstract: AIM: Despite widespread opioid use at a societal level, only a minority of individuals exposed to opiates progress to opioid use disorder (OUD). Can individuals predisposed to developing OUD upon opiate exposure be identified before first use? In this initial study, our objective was to develop an instrument that could accurately differentiate cohorts with different opiate-use statuses, laying the groundwork for predictively differentiating those at risk of OUD in a comprehensive, large-scale longitudinal study.
METHODS: We collected data for 27 well-validated instruments (550 individual questions) covering four risk domains: Overall Life Quality, Opioid-Induced Hedonic Experience, Genetic Predisposition, and Psychological Predisposition. We had 150 participants equally divided between three matched cohorts: those with a history of OUD, those exposed to opiates but with no history of OUD, and a control cohort with no exposure. Employing a two-step modeling process, we applied dimension reduction methods to our dataset comprising 550 data points per participant, and utilized linear discriminant analysis for classification. Our goal was to identify the minimal number of questions required to classify these cohorts.
RESULT: We were able to identify just 10-25 questions extracted from the 27 instruments that were, when combined together, able to separate the three cohorts with reasonable efficiency. Questions related to lifetime stress, coping, social support, reward responsiveness, and impulsivity emerged as influential in separating the cohorts. Accuracy rates were in the 80%-94% range for the training, and 70%-85% range for the testing data, for these 10-25 questions.
CONCLUSION: Using a between-subjects approach as an initial step, we were able to identify opiate-use status with high precision. This lays the groundwork for employing these features in a longitudinal predictive study. Such an approach holds promise for accurately identifying individuals at risk for OUD prior to first exposure, thereby contributing to the advancement of early intervention strategies.

Disclosures: A. Secmen: A. Employment/Salary (full or part-time):; *Supported by Behavioral Sciences Training in Drug Use Research. **S. Harley:** None. **P.W. Glimcher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); * Co-Investigator Paul Glimcher declares a potential conflict of interest. He holds significant stock in DataCubed Health which provided their app pro bono for this study..

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.10/Web Only

Topic: G.09. Drugs of Abuse and Addiction

Support: 5K01AA027833-04

Title: Association Between Chronic Pain and Poly-Substance Use: A Case-Control Study

Authors: *R. RIPON[1,2], N. MALEKI[3,2];
[1]Harvard Univ., Cambridge, MA; [2]Mass General Brighum, Boston, MA; [3]Dept. of Psychiatry, Harvard Med. Sch., Boston, MA

Abstract: Background: Chronic pain is a significant global health problem that frequently generates essential social, economic, and personal burdens. While chronic pain is considered a common co-occurring disorder with addiction, it is not established whether there is a link between chronic pain and polysubstance use, also known as the simultaneous use of multiple psychoactive substances. This study aims to examine the relationship between polysubstance use and chronic pain and identify risk factors associated with the use of polysubstance. Methods: This study of cases and controls included 573M participants in the National Health and Nutrition Examination Survey, divided into cases (polysubstance users) and controls (those with no history of substance use). Polysubstance use was defined as using 2 or more substances (Cocaine, Heroin, Methamphetamine, Marijuana) within the past three months. Chronic pain was defined as persistent pain, aching, or stiffness in specific body areas for six weeks or more. To evaluate the relationship between the use of polysubstance and chronic pain, a descriptive analysis and logistic regression models adjusted for demographics and several chronic health conditions were used. Results: 6.50% of participants are polysubstance users. Compared with 23.7% of non-substance users, 43.7% of polysubstance users reported chronic pain. Polysubstance users were more than twice as likely to experience chronic pain (OR = 2.5; 95% CI: 1.52 - 4.09; $P < 0.001$). There was a significant difference in the prevalence of substance use by sex; men had a three-fold increased risk (OR = 3.073; $P < 0.001$) of ploy-substance use. An educational disparity was evident with polysubstance use since people with lower secondary education were at higher risk than college graduates. According to additional findings, people with lower socioeconomic status and medical condition emphysema (OR: 9.28; $P = 0.027$) were also significantly more likely to be polysubstance users. Polysubstance use was also associated with higher odds of severe levels of depression (OR:1.52, P=0.009), whereas not having depressive symptoms was found to be less common in polysubstance users. Conclusion: The strong connection between polysubstance use and chronic pain demonstrates the need for comprehensive healthcare strategies that address both problems at the same time. Interventions should focus on high-risk groups identified by demographic and socioeconomic factors. More research is required to find these problems' causes and create effective prevention and treatment programs.

Disclosures: R. Ripon: None. **N. Maleki:** None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.11/L28

Topic: G.09. Drugs of Abuse and Addiction

Title: The association between the consumption of psychoactive substances and psychiatric disorders in polyconsumers at the juvenile integration center

Authors: K. LIMON BAÑUELOS[1], **V. HERNÁNDEZ FERNÁNDEZ**[1], I. LIMON PEREZ DE LEON[3], A.-L. GONZÁLEZ-NABOR[2], I. PLIEGO-PLIEGO[1], *A. OSORIO-ESPINOZA[4]; [1]Ctr. de Estudios Superiores de Tepeaca, Puebla, Mexico; [2]Ctr. de Estudios Superiores de Tepeaca, PUEBLA, Mexico; [3]Benemerita Univ. Autonoma De Puebla, Puebla, ; [4]CEST CENTRO DE ESTUDIOS SUPERIORES DE TEPEACA, PUEBLA, Mexico

Abstract: Dual pathology (DP) is defined as the coexistence of a substance use disorder (SUD) with another psychiatric disorder and may present in different ways, simultaneously, in the same individual over a specific period of time (Arias et al., 2013; Sánchez-Morate et al., 2017; Szerman et al., 2015). Although the etiological relationship that underlies this pathology is not entirely clear, it is believed that genetic, neurobiological, and epigenetic factors as well as the environment in which the individual is immersed are involved in its appearance (Szerman N, 2017; Szerman et al. al., 2013).A retrospective, longitudinal study was conducted on 130 patients aged between 12 and 24 years, in accordance with the corresponding selection criteria and applying the χ^2 statistical test and Fisher's exact test, with a confidence interval of 95% and a statistical significance of * p <0.05. The results obtained reveal that 119 (91.5%) patients from the sample group presented dual pathology, the majority of which were male, among whom marijuana was the most preferred psychoactive substance with 92.4%, followed by alcohol with 60.5%, amphetamines with 52.1%, and cocaine with 40.3%. The average age of the male subjects was 19.32 years ± 3.5. Nine subjects from (6.9%) the female population presented a possible dual pathology, with marijuana identified as the psychoactive substance of choice for 100% of this group, followed by amphetamines with 77.8%, alcohol with 55.6%, and cocaine with 33.3%, while the group's mean age was 18.44 years ± 4.30. The most statistically significant associations found were marijuana with depression (*P=0.0236), cocaine and amphetamines with anxiety and psychosis (***P=0.0003 and ***P=0.0001, respectively), and amphetamines and post-traumatic stress disorder (PTSD) (*P=0.0132) and the association between alcohol and attention deficit hyperactivity disorder (ADHD) (**P=0.0067).

Disclosures: K. Limon Bañuelos: None. **V. Hernández Fernández:** None. **A. González-Nabor:** None. **I. Pliego-pliego:** None. **A. Osorio-Espinoza:** A. Employment/Salary (full or part-time):; Centro de Estudios Superiores de Tepeaca.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.12/L29

Topic: C.10. Brain Injury and Trauma

Title: Comparing The Nuclear Volume of Dark and Healthy Neurons in Fentanyl Exposed Mice

Authors: V. V. VIZCAINO[1], D. GORMAN[1], G. WILDENBERG[2], N. B. KASTHURI[3], ***A. MASELLI**[1];
[1]Chicago State Univ., Chicago, IL; [2]Neurobio., Univ. of Chicago Dept. of Neurobio., Chicago, IL; [3]Neurobio., Univ. of Chicago, Chicago, IL

Abstract: Dark Neurons are characterized by a higher intensity staining in histological preparations. Fentanyl is a powerful synthetic opioid, and it is estimated to be about 50 to 100 times more potent than Morphine. Fentanyl is commonly used in medical settings for pain management, especially for severe pain, it is also a drug with a substantial potential for abuse. Research on the effects of opioids on the brain, particularly in animal models, has revealed that chronic opioid exposure can lead to changes in neuronal structure. This pilot study is designed to understand if there is a connection between Fentanyl exposure and the presence of Dark Neurons in mice. We are analyzing two volume electron microscopy datasets. The first volume dataset is from a mouse brain exposed to Fentanyl with an IP injection of 700 µg/kg. The second is a control dataset. In Fentanyl-exposed mice, we see a prevalence of neurons with an altered morphology, consistent with Dark Neurons. These cells have increased stain density, and their nuclei have lost the textbook oval cross-section becoming more irregular. We ask whether the nuclear volume changes by examining the volume of the nuclei. We calculate the volume by segmenting the neurons' nuclei, in both Fentanyl and the control datasets. We present observations on a potential connection between altered nuclear morphology and Fentanyl exposure. In the literature the Dark Neuron story is complex, some reports question the validity of Dark Neurons as bona fide biological structures suggesting they are artifacts of tissue processing.

Disclosures: V.V. Vizcaino: None. **D. Gorman:** None. **G. Wildenberg:** None. **N.B. Kasthuri:** None. **A. Maselli:** None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.13/L30

Topic: G.09. Drugs of Abuse and Addiction

Support: CSUBIOTECH Faculty-Student Research Development Award

Title: Impact of adolescent nicotine exposure on methamphetamine reward

Authors: J. RICHIE, A. LUJAN, A. MORA, M. AROCHE, D. Y. LOPEZ SANCHEZ, *C. CRAWFORD;
Psychology, California State Univ., San Bernardino, San Bernardino, CA

Abstract: Cigarette smoking and vaping are very common during adolescence, and most individuals who smoke begin during this developmental period. Tobacco use during this stage of development is not solely a result of social influences, such as peer pressure, because recent

research suggests that biological factors play a role during this period of increased vulnerability. In general, tobacco has a positive effect on mood and behavior, but the initial smoking engagement tends to be aversive]. Interestingly, adolescents experience more positive and fewer aversive effects than adults during their first smoke. Importantly, there is a correlation between adolescent nicotine use and later drug use, and nicotine has been suggested to act as a "gateway" to other drug use. For example, adolescent nicotine exposure is associated with adult psychostimulant and marijuana use. There are also clear preclinical sex differences in the reinforcing properties of both nicotine and methamphetamine (MA). During nicotine self-administration, female rats maintain a higher motivation to obtain nicotine than males. Similarly, female rats are more susceptible to the reinforcing properties of MA than male rats. In the current study, we will assess whether early adolescent exposure to nicotine will increase the rewarding properties of MA in late adolescent male and female rats using a conditioned place preference (CPP) procedure. Male and female Sprague-Dawley rats were injected with (0.16, 0.32, or 0.64 mg/kg, ip) once daily for 20 consecutive days beginning on postnatal day (PD) 25. On PD 45, methamphetamine-induced CPP was assessed using a 10-day biased CPP procedure consisting of one preconditioning day, eight conditioning days (consisting of alternating daily injections of saline or MA (0 or 1 mg/kg, ip), and one test day. Pre-exposure to nicotine (0.32 mg/kg) increased MA-induced activity in both male and female rats on the conditioning days. On the test day, Nicotine (0.64 mg/kg) exposure enhanced MA-induced CPP in males and females, but the effect was much stronger in females. Nicotine pretreatment (0.32 mg/kg) also increased the activity of female rats given MA during conditioning. These findings suggest that exposure to nicotine during adolescence alters the rewarding nature of MA. In addition, our results indicate that sex is an important factor to consider in assessing the effects of nicotine and may be essential for designing more effective prevention and treatment programs.

Disclosures: J. Richie: None. **A. Lujan:** None. **A. Mora:** None. **M. Aroche:** None. **D.Y. Lopez Sanchez:** None. **C. Crawford:** None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.14/L31

Topic: G.09. Drugs of Abuse and Addiction

Title: Long-term effects of adolescent nicotine and ethanol exposure on motivated behavior and cortical spine density

Authors: H. WEBBER[1], A. BALDWIN[1], K. R. J. LEWIS[2], P. C. SHERRILL[1], *G. M. FERNANDEZ[3];
[1]Neurosci., [2]Psychology, [3]Christopher Newport Univ., Newport News, VA

Abstract: Adolescent use of alcohol and nicotine is once again on the rise. Preclinical research demonstrates that drug exposure during early developmental stages can have long- term,

detrimental effects on learning and memory, as well as emotional regulation, in adulthood. We employed a rodent model of adolescent nicotine and ethanol exposure to examine the combined effects of these drugs on long-term nicotine preference, exploratory behavior, and anxiety-like behavior. Starting on postnatal day 28, male and female Sprague Dawley rats were exposed to either a subcutaneous injection of 0.4 mg/kg nicotine at a dose of 1 ml/kg and an intraoral gastric gavage of 20% v/v ethanol at a dose of 5 g/kg or combined saline injections and water gavage. All rats received a total of 12 exposures on an intermittent, 2 day on/ 2 day off schedule. Repeated nicotine and ethanol exposure did not affect time spent in the open arm of an elevated plus maze but did decrease locomotor activity and exploratory behavior. Female rats formed a preference for a unique environment that was paired with nicotine (single trial nicotine conditioned place preference), whereas male rats did not. In addition, females pre-treated with nicotine and ethanol formed a stronger preference for a nicotine- paired environment compared to nicotine and ethanol pre-treated males. Our findings indicate that sex plays a role in the long-term preference for nicotine, while adolescent nicotine and ethanol exposure influences exploratory behavior. Prefrontal cortical (infralimbic and prelimbic) spine density will be correlated with behavioral results, in addition to a nicotine only and ethanol only comparison group.

Disclosures: H. Webber: None. **A. Baldwin:** None. **K.R.J. Lewis:** None. **P.C. Sherrill:** None. **G.M. Fernandez:** None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.15/L32

Topic: G.09. Drugs of Abuse and Addiction

Support: UWRF Undergraduate Stipends and Expenses Grant
UWRF Faculty Research Grant

Title: The effect of adolescent social isolation stress on nicotine conditioned place preference, stress coping behavior, and dendrite remodeling.

Authors: A. D. SCHAEFER[1], S. SYMALLA[1], K. G. WAKEFIELD[1], A. SYED[1], ***D. G. EHLINGER**[2];
[1]Psychological Sci., [2]Univ. of Wisconsin-River Falls, River Falls, WI

Abstract: Adolescence is a sensitive period in brain development marked by increased susceptibility to the effects of chronic stress, which may enhance vulnerability to neuropsychiatric conditions such as depression and substance use disorders. In this study, we examine the effect of adolescent social isolation stress on coping behavior, nicotine reward, and dendrite remodeling. During adolescence (postnatal day P35-P49) or adulthood (P60-74), male and female C57BL/6J mice were exposed to either social isolation (SI) stress or standard rearing

(SR) conditions and four nicotine exposures (0.35mg/kg) during a nicotine conditioned place preference (CPP) procedure. On approximately P49 (adolescent) or P74 (adulthood), stress-coping behavior was examined following a 6-minute forced-swim test (FST), and brains were processed for analysis of dendrite structure via Golgi-Cox staining. Our behavioral results show that adolescent SI mice rapidly develop nicotine CPP compared to both SR mice and adult mice, exhibit increased levels of immobility in the FST, and that prior nicotine exposure during adolescent social isolation decreases immobility in the FST. Ongoing research is further examining adult groups for behavioral comparisons and aims to assess nicotine and stress-induced dendrite remodeling (dendritic spine density; dendrite branching and length) in the brains of nicotine treated SI versus SR mice in the ventral striatum, hippocampus, and amygdala. Collectively, our results suggest that adolescent social isolation stress enhances the rewarding effects of nicotine and negatively impacts stress-coping behavior. Ongoing analyses will help determine neurological correlates of adolescent susceptibility to the negative effects of chronic social isolation stress and inform our understanding of adolescent brain development and vulnerability. Acknowledgements: Funding for this project was generously provided by a University of Wisconsin-River Falls Undergraduate Stipends and Expenses grant (awarded to ADS, AS, & KGW) and Faculty Research Grant (awarded to D.G.E.).

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Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.16/L33

Topic: G.09. Drugs of Abuse and Addiction

Title: Long-term effects of maternal THC exposure on the physiological and behavioral characteristics of stress-sensitive and stress-resilient offspring

Authors: *M. MARI[1], A. BAGAEV[1], D. SUR[2], N. KOGAN[1], A. PINHASOV[1];
[1]Ariel Univ., Ariel, Israel; [2]Dermatol., Univ. of Wisconsin, Madison, Madison, WI

Abstract: Maternal exposure to drugs during pregnancy can lead to growth and morphological abnormalities, as well as changes in brain function and behavior in offspring. THC is a psychoactive and teratogenic compound found in cannabis. However, rodent and human studies show high heterogeneity in responses to cannabis exposure. Our observation demonstrates that stress coping abilities of the organism may play a critical factor in determining the response to cannabis exposure during pregnancy and early stages of postnatal development, as well as it is intra and transgenerational outcomes. This study aims to understand the impact of THC exposure during pregnancy on maternal attachment, offspring's epigenetic programming, and behavior parameters of selectively bred mice with strong characteristics of social dominance (Dom) and social submissiveness (Sub) exhibiting stress resilience or vulnerability respectively. Pregnant

Dom and Sub Dams were injected intraperitoneally THC (20mg/kg) or saline at gestational days 13,15, and 17. We found that prenatal exposure to THC increased sociability and reduced repetitive and anxiety-like behavior in sub-offspring, while reduced social performances in Dom counterparts. In addition, prenatal exposure to THC differentially affected brain neurochemistry hippocampal mRNA expression of genes related to dopaminergic signaling among Dom and Sub adult offspring. Thus, our study demonstrates that the outcomes of prenatal exposure to THC depend upon the stress-coping abilities of the organism, eliciting divergent effects on sociability and anxiety-like behavior through the intricate modulation of dopaminergic signaling. These observations emphasize the importance of considering these factors when examining the effects of THC, highlighting the intricate interplay between stress-coping abilities and cannabinoid exposure in shaping behavioral outcomes.

Disclosures: **M. Mari:** None. **A. Bagaev:** None. **D. Sur:** None. **N. Kogan:** None. **A. Pinhasov:** None.

Poster

PSTR039: Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.17/L34

Topic: G.09. Drugs of Abuse and Addiction

Support: P50-HD103525
Missouri S&T, Office of Vice Chancellor for Research and Innovation

Title: Exposure to e-cigarette (vaping) aerosols are neurotoxic to the developing mouse brain.

Authors: *K. K. NOGUCHI[1], C. PALMER[1], N. FUHLER[1], A. SCHARF[2];
[1]Psychiatry, Washington Univ. in St Louis, St Louis, MO; [2]Missouri Univ. of Sci. and Technol., Rolla, MO

Abstract: It is estimated that 4.9% of women use e-cigarettes (ECs) during pregnancy suggesting approximately 180,000 US children are born yearly who are exposed to the aerosolized chemicals in e-liquids (vaping juice). This exposure may increase due to several recent claims that EC use during pregnancy is a safer alternative than traditional combustion cigarettes (TCs). Importantly, ECs expose the user to high levels of chemicals not seen with TCs. In particular, ECs aerosolize two liquids (propylene glycol and glycerin) as a vehicle for nicotine delivery to the lungs. We have previously reported injections of propylene glycol (PG) dose-dependently increased apoptosis in the developing mouse brain. Interestingly, the pattern of neurodegeneration and age dependency was strikingly similar to that produced by ethanol exposure. To examine whether exposure to EC aerosols alone (without nicotine) can produce similar neurodegeneration, postnatal day 7 mouse pups (neurodevelopmental equivalent of the third trimester human fetus) were exposed to 3 hrs of intermittent EC aerosols for 1 second every 20 seconds. Aerosolized PG/glycerin (70%/30% mixture) was produced by connecting an EC to

a chamber (maintained at 30° C) applying a constant vacuum at 2.5-3.5 L/min similar to previous studies. A control group from the same litter was exposed to the same conditions with a constant vacuum of air only. After six hours, all animals were perfused and brains sectioned for immunolabeling with activated caspase-3 (a marker of cells irreversibly committed to apoptotic death). Cell counts revealed aerosol exposure significantly increased apoptotic density by 31% ($t[10] = 3.563$, $p = 0.0052$) or approximately 30,000 more apoptotic neurons per brain. These results suggest a single EC use 3 hrs or longer during pregnancy may be neurotoxic to the developing human fetus. This finding is particularly troubling since actual EC use may occur daily throughout pregnancy, women have impaired PG metabolism during pregnancy, and the placenta has an extremely limited ability to protect the fetus from PG.

Disclosures: K.K. Noguchi: None. **C. Palmer:** None. **N. Fuhler:** None. **A. Scharf:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.01/L35

Topic: G.09. Drugs of Abuse and Addiction

Support: 1K99DA056573
1K08DA055157

Title: Contribution of a distinct medium spiny neuron population to opioid withdrawal learning and behavior

Authors: *J. A. G. SOARES[1,2], M. B. POMRENZE[3], G. TOUPONSE[4], S. SUTLEY[4], N. ESHEL[4], R. C. MALENKA[3], J. TUCCIARONE[4];
[1]Stanford Univ., Stanford, CA; [2]Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA; [3]Nancy Pritzker Lab., Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA; [4]Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA

Abstract: The opioid epidemic is a devastating public health issue that has intensified over the past two decades with over 106,000 overdose deaths in 2021 alone. Identifying the brain circuits vulnerable to the action of opioids can inform the development of therapeutic strategies that target dependence and relapse. The μ-opioid receptor (MOR) is a main target of opioids and is highly expressed in the nucleus accumbens (NAc)–a regulator of the mesolimbic dopamine (DA) system. Previous work has revealed the existence of a MOR+ medium spiny neurons (MSN) population encoding negative valence and aversion characterized by expression of the transcription factor *Teashirt1 (Tshz1)*. In this study, we hypothesized that the *Tszh1+* MSN population plays an important role in aversion learning during opioid withdrawal. By manipulating *Tshz1+* neurons we aimed to 1) determine their role in regulating mesolimbic DA release during precipitated opioid withdrawal and to 2) delineate their contribution to the aversive learning associated with withdrawal states. Optogenetic stimulation of NAc *Tshz1+*

MSNs led to a rapid and reversible inhibition of dopaminergic signals and negative valence. Chemogenetic inhibition of this population blunted withdrawal conditioned place aversion (CPA). Conditional KO of MORs in *Tszh1+* neurons in the NAc did not alter cardinal somatic symptoms associated with withdrawal, but reduced precipitated withdrawal CPA. Together, our data suggest the existence of a unique population of NAc neurons that mediate aversion learning during acute opioid withdrawal through strong modulation of mesolimbic DA release. Ongoing work in our lab aims to map the c-fos and neural activity of *Tszh1+* MSNs during withdrawal. Additionally, we will identify the role for other MOR rich circuit nodes (central amygdala and habenula) during naloxone-precipitated withdrawal to compare with the influence of *Tshz1+* NAc MSNs. This more elaborated circuit dissection could have important implications in negative reinforcement and states of physical and emotional suffering that drives opioid relapse.

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Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.02/L36

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA P01DA047233
NIDA R01DA014133

Title: Homecage oral oxycodone self-administration induces preference and differential gene expression in the prefrontal cortex and nucleus accumbens of mice

Authors: *B. T. KIPP[1], T. M. GYLES[2], L. HOLT[3], E. J. NESTLER[4];
[1]Icahn Sch. of Med. at Mount Sinai, New York City, NY; [2]Friedman Brain Inst., Icahn Sch. of Med. At Mount Sinai, New York, NY; [3]Neurosci. Dept., Mount Sinai Sch. of Med., New York, NY; [4]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Opioid use disorder (OUD) continues to be a complex and burgeoning healthcare issue with an estimated annual cost greater than $700 Billion USD in 2018, and an increasing rate of overdose deaths in the years since. Prescription opioids have contributed to the ongoing opioid epidemic and remain a potent gateway drug in substance use disorders. Among prescription opioids, oxycodone appears to have a greater abuse potential due to, in part, higher likeability scores and fewer adverse side effects compared to other opioids. Here, we sought to characterize a homecage prescription opioid use model by measuring behavioral and transcriptional changes following oral oxycodone self-administration (OSA). Singly housed adult

male and female C57BL/6J mice were exposed to increasing oxycodone concentrations in their drinking water for 5 days followed by 14 days of 1 mg/mL oxycodone two-bottle choice or water (CON). OSA males and females exhibited preference to oxycodone and escalated their intake during the two-bottle choice phase. Moreover, we demonstrate signs and symptoms of physical dependance in OSA mice following naloxone precipitated withdrawal that were absent in CON animals. In a separate cohort of mice, bulk-RNAseq was used to measure differential gene expression in the prefrontal cortex and nucleus accumbens of OSA and CON mice, identifying molecular and cellular targets for future intervention. In summary, this model recapitulates certain essential features of opioid addiction, and offers an interesting avenue for understanding the formation of prescription opioid dependance in clinical populations.

Disclosures: **B.T. Kipp:** None. **T.M. Gyles:** None. **L. Holt:** None. **E.J. Nestler:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.03/L37

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA Grant P01DA047233

Title: Identification of Mbd3 as a Key Hub Gene in Nucleus Accumbens After Heroin Self-Administration and Relapse in Mice

Authors: *R. FUTAMURA[1], C. J. BROWNE[2], A. M. MINIER-TORIBIO[3], X. CHEN[4], A. RAMAKRISHNAN[5], Y. YIM[3], M. SALERY[6], A. GODINO[3], L. SHEN[1], Y. L. HURD[1], B. ZHANG[1], E. J. NESTLER[2];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Nash Family Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Inst. for Genomic Med., Columbia Univ. Program In Neurobio. And Behavior, New York, NY; [5]Mount Sinai Sch. of Med., New York, NY; [6]Nash Family Dept. of Neurosci. & Friedman Brain Inst., Mount Sinai, New York, NY

Abstract: Repeated opioid exposure causes epigenetic changes throughout the brain reward circuitry, which are hypothesized to promote relapse susceptibility. Of note, shifts in the DNA methylation landscape within the nucleus accumbens (NAc)—a brain region involved in mediating motivation and reward processing—have been linked to compulsive drug-seeking and drug-taking behaviors characterized by relapse upon re-exposure to the drug or context related-cues. Recently, our laboratory established broad patterns of transcriptional regulation across six brain reward regions that are driven by volitional drug-taking and -seeking behaviors using intravenous heroin self-administration (SA) in mice (Browne et al, Sci Adv, PMID: 37294757). To identify gene networks regulating relapse in this model, we utilized multiscale embedded gene co-expression network analysis (MEGENA) of this RNA-sequencing (RNA-seq) dataset,

which revealed a gene network in the NAc highly enriched with genes upregulated by heroin-primed drug-seeking. Within this network, we found methyl-CpG binding domain protein 3 (Mbd3) to be the strongest hub gene; Mbd3 was not only one of the most upregulated genes in this condition but also positively associated with addiction-like behavior from exploratory factor analysis. Preliminary data show that viral manipulation of Mbd3 in all NAc neurons controls rewarding responses to opioid exposure. Ongoing efforts include determining the cell-type-specificity of Mbd3 regulation in D1- or D2- medium spiny neurons (MSNs) in the NAc and using viral approaches to assess how Mbd3 in each cell type influences drug-seeking behavior in relapse. Further, whole genome bisulfite sequencing (WGBS) is underway to examine how opioid exposure shifts the DNA methylation landscape within the NAc which will then allow us to correlate transcriptomic and methylomic data to ultimiately determine convergent regulatory mechanisms implicated in opioid use disorder (OUD) pathogenesis.

Disclosures: **R. Futamura:** None. **C.J. Browne:** None. **A.M. Minier-Toribio:** None. **X. Chen:** None. **A. Ramakrishnan:** None. **Y. Yim:** None. **M. Salery:** None. **A. Godino:** None. **L. Shen:** None. **Y.L. Hurd:** None. **B. Zhang:** None. **E.J. Nestler:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.04/M1

Topic: G.09. Drugs of Abuse and Addiction

Title: A novel role of submedius thalamus and its projections to orbitofrontal cortex in incubation of oxycodone craving after forced abstinence

Authors: *H. LIN[1], J. STRAUCH[1], X. LUO[1], M. BURKE[1], X. LI[1,2];
[1]Univ. of Maryland, College Park, MD; [2]Program in Neuroscience and Cognitive Science, University of Maryland, College Park, MD

Abstract: Prescription opioids are the main driver of the opioid epidemic that involves drug misuse, addiction, and even overdose death. The high relapse rate is a major challenge in treating drug addiction, including oxycodone. In rats, oxycodone seeking progressively increases during abstinence and maintains for an extended period, a phenomenon termed incubation of oxycodone craving. We previously found that the orbitofrontal cortex (OFC) plays a causal role in this incubation after forced abstinence. Here, we aimed to identify critical upstream regions of OFC in incubation of oxycodone craving by focusing on the submedius thalamus (Sub), a poorly understood thalamic area. We first used the pharmacological inactivation approach to examine whether Sub alone is critical in incubated oxycodone seeking. After oxycodone self-administration training (6 h/d for 10 d), we injected a mixture of muscimol + baclofen (3 + 20 ng/ 0.3 µl/side) into Sub 15 min before the oxycodone-seeking test on abstinence day 15. We found that pharmacological inactivation of Sub decreased incubated oxycodone seeking. Next, we combined fluorescence-conjugated cholera toxin subunit B (CTb-488, injected into OFC) and

Fos (a neural activity marker) to examine whether activation of Sub to OFC projection is associated with incubated oxycodone craving. We first injected CTb-488 ipsilaterally into OFC and trained rats for oxycodone self-administration. On abstinence day 15, we either tested (Seeking-test) or did not test (No-test) rats for oxycodone seeking. Immediately after the test, we perfused the rats for immunohistochemistry to label Fos in Sub. We found that the number of Fos + CTb double-labeled cells in Sub was significantly higher in Seeking-test group than No-test group on abstinence day 15. Taken together, our data showed that Sub played a critical role in incubated oxycodone seeking, and the activation of Sub◊OFC projections was associated with oxycodone seeking on abstinence day 15. Ongoing studies are using the chemogenetic approach to study the role of Sub to OFC projections in incubation of oxycodone craving after forced abstinence.

Disclosures: H. Lin: None. **J. Strauch:** None. **X. Luo:** None. **M. Burke:** None. **X. Li:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.05/M2

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant 1R21DA058805-01

Title: Mitochondrial morphology in orbitofrontal cortical neurons during incubation of oxycodone craving

Authors: *C. MATHESON[1,2], X. LUO[1], A. OLANIRAN[1], M. BURKE[1], H. LIN[1], X. LI[1,2]; [1]Dept. of Psychology, [2]Neurosci. and Cognitive Sci., Univ. of Maryland, College Park, MD

Abstract: Relapse is a major challenge in treating opioid addiction, including oxycodone, a commonly abused prescription opioid. In rats, cue-induced oxycodone seeking progressively increases during abstinence. Our previous work demonstrated that orbitofrontal cortex (OFC) plays a critical role in this incubation of oxycodone craving. However, the molecular mechanisms in OFC that contribute to this incubation are unknown. Here, we focus on mitochondrial dynamics in OFC and characterize the mitochondrial morphology in OFC neurons during incubation of oxycodone craving. We used a dual-virus approach to sparsely label mitochondria in OFC neurons by injecting the adeno-associated virus (AAV)-hSyn-GFP together with AAV-CMV-mitoDsRed bilaterally into OFC. Next, we trained male rats to either self-administer saline (as the control group) or oxycodone (0.1 mg/kg/infusion) for 6 h/day over 10 days. On abstinence day 15, we perfused both groups of animals and processed the brain for confocal microscopy. Our image analysis showed that in the somas of OFC neurons, there was a significant increase in the size-frequency of the smallest mitochondria, accompanied by overall increased mitochondria density, in oxycodone rats compared with saline rats. This finding suggests that mitochondria in OFC neuronal cell bodies enhanced fission after 15-day abstinence

from oxycodone self-administration. In contrast, we did not observe the differences in primary dendrites of OFC neurons between the two groups. Studies are underway to examine whether enhanced mitochondrial fission in OFC somas is time-dependent after abstinence and whether there are sex differences in mitochondrial morphology during incubation of oxycodone craving.

Disclosures: C. matheson: None. **X. Luo:** None. **A. Olaniran:** None. **M. Burke:** None. **H. Lin:** None. **X. Li:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.06/M3

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA Grant R01DA012513-22

Title: Cell and circuit specific modulation of heroin consumption in the ventral pallidum

Authors: *V. OWONA AYISSI[1], P. W. KALIVAS[2], B. N. KUHN[3];
[1]Med. Univ. of South Carolina, Charleston, SC; [2]Neurosci. Res., Med. Univ. S Carolina, Charleston, SC; [3]Dept. of Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Substance use disorder is a chronic neuropsychiatric disorder whereby compulsive drug seeking and relapse occurs regardless of attempts to refrain from drug use. Considerable scientific progress has been made toward disentangling the complex neurobiological mechanisms underlying addiction-related behaviors. However, the neurobiological basis of drug seeking versus refraining (i.e. withholding from drug seeking) has yet to be thoroughly assessed. The ventral pallidum (VP) exhibits opposing regulation of appetitive and aversive motivated behaviors, with the dorsolateral (dl) sub-compartment explicitly showing cell-specific regulation over cocaine seeking versus refraining behavior. In the current studies, male and female transgenic mice expressing Cre recombinase selectively in either GABA, enkephalin or glutamate cells underwent heroin self-administration training (12 days), followed by a week of forced abstinence and extinction training (12 sessions). Tests for cued reinstatement then followed using a within-subject design. In the first study, a Cre-dependent inhibitory Gi DREADD (designer receptor exclusively activated by designer drugs) was injected in the dlVP. Selective chemogenetic inhibition of dlVP GABA or enkephalin cells prevented cue-induced reinstatement of heroin-seeking, whereas dlVP glutamate neuron inhibition promoted relapse. These results compliment previous findings identifying dlVP cell-specific regulation of cocaine-seeking behavior. Next, an intersectional chemogenetic approach was used to assess the contribution of cell-specific dlVP efferent pathways in mediating heroin seeking versus refraining behaviors. Current results show that inhibition of dlVP GABAergic projections to the subthalamic nucleus, a region involved in reward seeking, reduces cued heroin seeking behavior. In contrast, chemogenetic inhibition of dlVP glutamatergic projections to the lateral

hypothalamus, a critical component of the motive circuitry, enhanced heroin seeking. Ongoing work is assessing the functional role of dlVP enkephalin projections to the subthalamic nucleus. Additional work using viral tracing is identifying alternative dlVP cell-specific projections that may contribute to these opposing behaviors. Together, these results emphasize the cell and pathway-specific functional regulation of the dlVP in mediating heroin seeking and refraining, contributing to our understanding of the neurobiology of heroin relapse.

Disclosures: V. Owona ayissi: None. **P.W. Kalivas:** None. **B.N. Kuhn:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.07/M4

Topic: G.09. Drugs of Abuse and Addiction

Support: OHSU startup funds to MEW

Title: Incubation of oxycodone craving: electrophysiological and chemogenetic studies of the pathway from paraventricular nucleus of the thalamus to the nucleus accumbens

Authors: *H. KUHN, E.-K. HWANG, S. J. WEBER, M. M. BEUTLER, A. M. WUNSCH, M. E. WOLF;
Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: A major problem in treating opioid use disorder is persistence of craving after protracted abstinence. This has been modeled in rodents using the incubation of craving model, in which cue-induced drug seeking increases over the first weeks of abstinence from drug self-administration and then remains high for an extended period. Incubation has been reported for many drugs of abuse, including oxycodone.We previously showed that expression of oxycodone incubation is blocked on forced abstinence day 15 (AD15) or AD30 by intra-nucleus accumbens (NAc) core or shell injection of Naspm, a selective antagonist of calcium-permeable AMPA receptors (CP-AMPARs), suggesting that CP-AMPARs upregulate during oxycodone incubation. Principal neurons of the NAc are D1 and A2a receptor-expressing medium spiny neurons (MSN; A2a and D2 receptors colocalize). D1 and A2a MSN are implicated in different aspects of motivated behavior. These MSN receive glutamate inputs from many regions, including the paraventricular nucleus of the thalamus (PVT). The PVT-NAc pathway has been implicated in both rewarding and aversive behaviors. The purpose of this study is: 1) to determine the role of PVT-NAc core and shell pathways in expression of oxycodone incubation, and 2) characterize incubation-related plasticity in PVT-D1 and PVT-A2a MSN synapses with a focus on CP-AMPARs.For chemogenetic studies, wild-type rats received AAV-hM4Di (inhibitory DREADD) infusion in the posterior PVT to drive expression in PVT-NAc neurons. Rats then underwent long-access oxycodone self-administration (6 h/day for 10 days) and a cue-induced drug seeking test on AD15 (after incubation has plateaued). Prior to the seeking test,

vehicle or clozapine-N-oxide (CNO) was infused into core or shell. Preliminary results indicate augmentation of cue-induced seeking after CNO infusion into core (*$p<0.05$). Preliminary electrophysiological studies in wild-type rats indicated CP-AMPAR upregulation, assessed using the rectification index and Naspm sensitivity, in PVT-shell but not PVT-core MSN after oxycodone incubation. To study this in a cell-type specific manner, D1-cre and A2a-cre rats crossed with a reporter line received infusion of AAV-ChR2 in the posterior PVT to drive opsin expression in PVT-NAc synapses. These rats underwent the same self-administration regimen described above. Whole cell recordings in visually identified D1 and A2a MSN, using light to optically activate PVT terminals in NAc, are underway. Male and female rats were used in all experiments.

Disclosures: H. Kuhn: None. **E. Hwang:** None. **S.J. Weber:** None. **M.M. Beutler:** None. **A.M. Wunsch:** None. **M.E. Wolf:** Other; Founder of Eleutheria Pharmaceuticals LLC.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.08/M5

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA-IRP

Title: Role of claustrum in incubation of opioid seeking after electric barrier-induced voluntary abstinence in male and female rats

Authors: *K. NEGISHI[1], Y. DUAN[2], A. BATISTA[2], M. PISHGAR[2], K. CALDWELL[2], S. CLAYPOOL[2], D. J. REINER[2], J. M. BOSSERT[2], Y. YANG[2], Y. SHAHAM[2], I. FREDRIKSSON[3];
[1]NIH, Natl. Inst. on Drug Abuse (NIDA), BALTIMORE, MD; [2]IRP/NIDA/NIH, Baltimore, MD; [3]Linköping Univ., Linköping, Sweden

Abstract: Background: We previously found that opioid seeking progressively increases or incubates after voluntary abstinence induced by adverse consequences of drug seeking. We also found that ventral subiculum (vSub) activity is critical to incubation of oxycodone seeking after electric barrier-induced abstinence. Here, we studied role of vSub afferents in this new form of incubation of oxycodone seeking.
Methods: We trained rats to self-administer oxycodone (6-h/day, 14-days) and then induced voluntary abstinence by exposing them to an electric barrier for 2 weeks. We used retrograde tracing (cholera toxin B subunit; CTb) combined with the activity marker Fos to identify projections to vSub that are active during 'incubated' relapse to oxycodone seeking (abstinence day 15 test). We then used muscimol-baclofen (GABAa + GABAb receptor agonists) reversible inactivation to determine the causal role of the claustrum in incubated relapse after electric barrier- or palatable food choice-induced abstinence. We also analyzed resting-state functional

connectivity of an existing functional MRI dataset to determine if functional connectivity changes in claustrum-related circuits predict incubation of oxycodone seeking.
Results: Claustrum neurons projecting to vSub were activated during the relapse test after 2 weeks of electric barrier-induced abstinence. Muscimol-baclofen inactivation of claustrum decreased incubation of oxycodone seeking after electric barrier-induced but not food choice-induced abstinence. Functional connectivity changes in claustrum-frontal and claustrum-striatal circuits during electric barrier-induced abstinence predicted incubated oxycodone relapse.
Conclusions: Our study demonstrates a novel role of the claustrum, a region involved in diverse psychological and physiological processes, in relapse to opioid drugs after abstinence induced by adverse consequences of drug seeking.

Disclosures: K. Negishi: None. **Y. Duan:** None. **A. Batista:** None. **M. Pishgar:** None. **K. Caldwell:** None. **S. Claypool:** None. **D.J. Reiner:** None. **J.M. Bossert:** None. **Y. Yang:** None. **Y. Shaham:** None. **I. Fredriksson:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

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Program #/Poster #: PSTR040.09/M6

Topic: G.09. Drugs of Abuse and Addiction

Support: 1ZIADA000434-23
FI2GM142476

Title: Effect of repeated opioid dependence and withdrawal on operant social interaction

Authors: *J. J. CHOW, K. M. PITTS, Y. SHAHAM;
NIDA IRP, Baltimore, MD

Abstract: Background: Opioid addiction is associated with decreased social connections. We recently reported that in male rats, but not female rats, operant responding for access to a social peer is higher for the opposite-sex peer than for the same-sex peer (Chow et al. J Neurosci, 2024). Here, we tested in both sexes the effect of opioid dependence and withdrawal on operant social interaction for the same- vs. opposite-sex peer.
Methods: We trained rats (n=24; 12 females) to lever-press for access to same- or opposite-sex peer (15-s access, fixed ratio (FR) 1 schedule for 45-min, 5-d/per sex). Next, we measured operant social interaction with either same- or opposite-sex peer during exposure to a dependence-inducing regimen of morphine exposure: twice daily (7-8 h apart) ascending morphine doses (0, 10, 20, 40, 60, and 80 mg/kg, s.c, 2 days per dose). We also measured operant social interaction after termination of morphine exposure (withdrawal phase, 6 days).
Results: As in our previous study, operant social interaction was higher for opposite-sex vs. same-sex in males but not females. Independent of the peer sex, morphine exposure decreased operant social interaction more strongly in males than in females. In both sexes, morphine

exposure decreased operant social interaction more strongly for same-sex vs. opposite-sex peer. Operant social interaction recovered after cessation of morphine exposure.
Conclusion: Pending an independent replication, results suggest that males and same-sex social interactions are more susceptible to the inhibitory effect of opioid dependence on social interaction.

Disclosures: J.J. Chow: None. **K.M. Pitts:** None. **Y. Shaham:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.10/M7

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA/NIH Grant R00DA048974 to GG

Title: Contribution of the prelimbic cortex to paraventricular thalamus pathway to heroin relapse

Authors: *A. L. JENSEN[1,2], N. J. HUSTON[1], G. GIANNOTTI[1];
[1]Integrative Physiol. and Neurosci., Washington State Univ., Pullman, WA; [2]Washington State University, Dept. of Integrative Physiol. and Neurosci., Pullman, WA

Abstract: Opioid use disorder (OUD) is a major public health concern that has seen a drastic increase in overdose rates post-pandemic. Relapse to opioid use often occurs to alleviate the aversive states associated with withdrawal. The paraventricular nucleus of the thalamus (PVT) plays a crucial role in the neural circuitry of substance use disorders in both humans and rodents. The prelimbic cortex (PL) is the major source of glutamatergic inputs to the PVT, and the PVT→PL pathway has recently been shown to be necessary for the retrieval of withdrawal memories in opioid-withdrawn mice following non-contingent morphine administration. However, it is unknown whether this pathway contributes to heroin withdrawal states and heroin relapse in a rat self-administration model. Therefore, here we employed heroin self-administration and chemogenetics to investigate the necessity of the PL→PVT pathway in relapse and withdrawal-mediated states following abstinence from self-administered heroin. We used a dual virus strategy, injecting AAVrg-Cre into the PVT and DIO-hM4Di-DREADD into the PL, to chemogenetically inhibit activity in this pathway. After recovery, rats were trained to self-administer heroin for 12 days, starting on a fixed-ratio (FR) 1 schedule for 7 days, progressing to FR2 (2 days), and ending on FR4 (3 days). Following 14 days of home-cage abstinence, rats underwent a cued relapse test, during which cues were present, but no heroin was delivered. Fifteen minutes before the test, rats received an injection of the high-affinity DREADD ligand J60 or a vehicle. Withdrawal somatic signs were detected using a supervised machine-learning pipeline by video recording the animals for 10 minutes, starting 5 minutes after either J60 or vehicle pretreatment. We found that chemogenetic inhibition of the PL→PVT pathway significantly reduced relapse rates during the cued relapse test. Moreover, chemogenetic

inhibition of this pathway attenuated heroin withdrawal-mediated somatic signs, although this reduction was not statistically significant compared to the vehicle-treated animals. Finally, we found that the total number of withdrawal signs positively correlated with the individual propensity to relapse (i.e., the number of active lever presses). To validate the functionality of the inhibitory hM4Di-DREADD, we performed whole-cell patch clamp recordings and found that bath application of J60 significantly reduced the excitability of PL neurons expressing hM4Di. Overall, our findings show that the PL→PVT pathway is necessary for cued relapse following abstinence from self-administered heroin and identify this pathway as a potential therapeutic target for OUD.

Disclosures: A.L. Jensen: None. **N.J. Huston:** None. **G. Giannotti:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.11/M8

Topic: G.09. Drugs of Abuse and Addiction

Title: Involvement of orexin 2 receptors (OX2R) within the CA1 area in the acquisition and expression of methamphetamine place preference

Authors: *R. AZIZBEIGI[1], F. MOSHREFI[2], A. HAGHPARAST[2];
[1]Dept. of Basic Sci., Sanandaj Br., Islamic Azad Univ., Sanandaj, Iran, Sanandaj, Iran, Islamic Republic of; [2]Neurosci. Res. Ctr., Shahid Beheshti Univ. of Med. Sci., Tehran, Iran, Islamic Republic of

Abstract: Treatment of Methamphetamine (METH) use disorder has become a crucial public health issue. The orexin system manipulation has provided promising evidence to attenuate addictive-like behaviors. This study explored the role of the orexin 2 receptor (OX2R) in the CA1 area of the hippocampal formation in the acquisition and expression of METH-induced place preference. Animals were subjected to bilateral administration of different dosages (1, 3, 10, and 30 nmol/0.5 µl DMSO per side) of a selective OX2R antagonist, TCS OX2 29 into the CA1 area throughout the conditioning phase or once on the post-conditioning phase in separate control and experimental groups. Behavioral data revealed that OX2R (10 nmol; $P < 0.05$ and 30 nmol;$P < 0.001$) antagonism during the conditioning phase could block the formation of METH place preference dose-dependently. In addition, intra-CA1 administration of TCS OX2 29 only at the highest dosage (30 nmol) declined the expression of METH place preference ($P < 0.01$). It was also indicated that the suppressive effects of orexin receptor blockade on the METH-seeking behavior in the CA1 area were anatomically specific to this area. These findings support the possibility of targeting the orexin system to develop novel and successful pharmacological options for the treatment of METH dependence.

Disclosures: R. Azizbeigi: None. **F. Moshrefi:** None. **A. Haghparast:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.12/M9

Topic: G.09. Drugs of Abuse and Addiction

Title: Identifying critical MOR-expressing neuronal subsets in opioid addiction

Authors: *H. JUNYAN[1], Z.-Q. XIONG[2];
[1]Ctr. for Excellence in Brain Sci. and Intelligence Technol., Shanghai, China; [2]Inst. Neurosci, Shanghai, China

Abstract: Opioids are highly addictive drugs that are responsible for a significant number of deaths related to drug abuse. It has long been believed that opioids act on GABAergic neurons with Mu-opioid receptors (MORs) in the ventral tegmental area, leading to the disinhibition of dopamine neurons and ultimately resulting in the rewarding and addictive effects of the drug. However, recent experimental findings have challenged this traditional hypothesis. Here we show that glutaminergic neurons with MORs expression may exert a more prominent influence on development and maintenance of opioid addiction compared to GABAergic neurons with MORs expression. This is supported by the experiment that glutaminergic neurons expressing MORs are involved in the regulation of dopamine levels in the nucleus accumbens medial shell following opioid administration, a key region in the reward pathway. Furthermore, glutamatergic neurons located in the thalamus could potentially be implicated in the initiation of opioid addiction. These findings suggest that glutamatergic neurons expressing MORs in the thalamus may play a pivotal role in the development of opioid addiction. This challenges the conventional understanding of the neurobiological mechanisms underlying opioid addiction and paves the way for further research in this area.

Disclosures: H. Junyan: None. **Z. Xiong:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

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Topic: G.09. Drugs of Abuse and Addiction

Support: CIHR PJT-186231

Title: The role of corticotropin-releasing factor in acute food deprivation-induced relapse to heroin seeking after punishment-imposed abstinence in rats

Authors: *D. MORALES[1], S. DORRANCE[1], E. PAGE[1], E. G. AH-YEN[1], C. BORGES[1], U. SHALEV[2];
[1]Concordia Univ., Montréal, QC, Canada; [2]Dept. of Psychology, Concordia Univ., Montreal, QC, Canada

Abstract: Relapse is a major challenge for the treatment of substance use disorders (SUD). One of the most significant triggers to relapse is stress. Previous findings suggest a critical role for extra-hypothalamic corticotropin-releasing factor (CRF) in stress-induced relapse. However, much of this evidence was obtained using relapse models in animals that were criticized for their limited relevance to the human condition. The study we present here, aims to understand the impact of CRF on acute food deprivation-induced relapse following punishment-imposed abstinence in rats. Rats were trained to self-administer heroin under a modified seeking-taking chain schedule, with continuous 5-minute drug access to the take lever. Abstinence was achieved using a probabilistic footshock punishment of seeking, followed by acute food deprivation as a relapse trigger. Preceding heroin-seeking relapse tests, CRF-receptor antagonist injections were administered intracerebroventricularly. Extended drug access allowed us to amplify taking behavior and better model heroin brain concentrations changes observed in humans. Preliminary data show robust heroin seeking and taking. Treatment with a CRF-receptor antagonist resulted in a noteworthy reduction in seek lever responses among food-deprived rats, suggesting a potential attenuation effect. Exploring the role of CRF in an ecologically relevant animal model, contributes to advancing our understanding of stress-induced relapse mechanisms. Positive results would enable the continued utilization of this model to identify relevant brain circuits associated with stress-induced relapse, while negative results would indicate improved ecological validity of the punishment-imposed abstinence procedure compared to existing stress-induced relapse models, such as the reinstatement procedure.

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Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

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Topic: G.09. Drugs of Abuse and Addiction

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Title: Social bonding and opioid modulation insights from prairie voles

Authors: *T. MUNGUIA-VILLANUEVA[1], F. CAMACHO[1], R. G. PAREDES[1,2], D. GASCA[1], N. F. DIAZ[3], R. E. MERCADILLO[4], W. PORTILLO[1];
[1]Inst. de Neurobiologia de la Univ. Nacional Autonoma de Mexico, Querétaro, QRO, Mexico; [2]Escuela Nacional de Estudios Superiores, Univ. Nacional Autonoma de Mexico, Querétaro, QRO, Mexico; [3]Inst. Nacional de Perinatologia, Mexico City, Mexico; [4]Unidad Iztapalapa, Univ. Autónoma Metropolitana, Mexico city, Mexico

Abstract: Opioids can influence long-term relationships significantly. The presence of stable and robust relationships with a sexual partner correlates with increased duration of participation in drug rehabilitation programs. Conversely, the dynamics of a couple's relationship can be altered by opioid addiction and withdrawal. Prairie voles, socially monogamous rodents known for forming pair bonds that endure until death, offer a relevant animal model for exploring the social dimensions of opioid abuse. This study aimed to: a) Investigate whether morphine (an opioid agonist) affects the formation and maintenance of pair bonds in male voles, and b) Assess the protective effects of socio-sexual relationships against opioid-addictive behaviors. The morphine-induced reward state was evaluated using the conditional place preference (CPP) test, while pair bond formation was assessed through the partner preference test, and maintenance was determined by observing aggressiveness towards foreign voles.
Regarding the first objective, our data demonstrate that a dose of 1mg/kg of morphine induces positive affective states, as indicated by the CPP test, without causing motor alterations in male prairie voles. Morphine also facilitates pair bond formation but does not impact its maintenance. Concerning the second objective, our results suggest that morphine injections did not induce a reward state in male voles cohabitating with other males. However, for voles cohabitating with females and forming a pair bond, morphine does induce conditioning. Consequently, opioids promote pair bond establishment and cohabitation with males but not with females, thus shielding voles from the addictive effects of opioids.

Disclosures: T. Munguia-Villanueva: 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.; Conahcyt CF-2023-G-206, IN204824, INPER2022-1-13. **F. Camacho:** None. **R.G. Paredes:** None. **D. Gasca:** None. **N.F. Diaz:** None. **R.E. Mercadillo:** None. **W. Portillo:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.15/M11

Topic: G.09. Drugs of Abuse and Addiction

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Title: Sex-dependent effects of oxycodone self-administration on decision-making functions in Long Evans rats

Authors: *S. G. SIMPSON[1], J. HILL[1], M. BAKIS[1], S. LAM[1], K. LAROCCO[2], P. VILLIAMMA[3], M. RUSSELL[4], M. BONILLA[1], S. M. GROMAN[1];
[1]Anesthesia and Critical Care, Univ. of Chicago, Chicago, IL; [2]Univ. of Minnesota, Twin Cities, St Paul, MN; [3]Neurosci., [4]Univ. of Minnesota, Minneapolis, MN

Abstract: Opioids remain the primary driver of drug-related deaths, and it is estimated that 5-20% of individuals prescribed medications such as oxycodone will develop opioid use disorder. Reliably identifying individuals at risk for developing an opioid addiction remains difficult, but our recent work has suggested that decision-making could serve as a biomarker of addiction susceptibility. Moreover, emerging evidence suggests that females are at greater risk for developing an opioid addiction compared to males. We hypothesized that greater drug-induced decision-making deficits would be associated with escalation in oxycodone use, and that this effect would be stronger in female rats compared to males. To test this hypothesis, decision-making functions were assessed in Long Evans rats (78 female, 78 male) using a three-choice, probabilistic reversal learning task. Rats were then trained to orally self-administer oxycodone (N=115) or vehicle (N=41) in three-hour daily sessions for 32 days followed by tests of motivation, extinction, and reinstatement. Decision-making functions were then reassessed and performance compared between experimental groups and sex. Escalation in oxycodone use was quantified using a power function. Preliminary analyses indicated that decision-making functions assessed prior to self-administration were attenuated in females, and that female rats self-administered greater amounts of oxycodone when compared to males. Oxycodone disrupted decision-making functions in males, whilst this effect was absent in female rats. These data suggest that decision-making plays a critical role in opioid addiction but may do so differently between sexes: pre-existing decision-making deficits in females may encourage greater oxycodone use, whereas drug-induced decision-making deficits in males may lead to problematic oxycodone-taking behaviors. Ongoing computational and molecular analyses will identify the reinforcement learning and genomic mechanisms that mediate these sex-dependent effects on decision-making.

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Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.16/M12

Topic: G.09. Drugs of Abuse and Addiction

Title: Sex-specific linear ubiquitination regulates cue-induced heroin seeking

Authors: *A. JEFFERS[1], K. LOOSCHEN[2], T. J. JAROME[3], S. MITRA[4];
[1]Oklahoma State Univ. Ctr. for Hlth. Sci., Tulsa, OK; [2]Marshall Univ., Huntington, WV; [3]Virginia Technol., Blacksburg, VA; [4]Pharmacol. and Physiol., Oklahoma State Univ. Ctr. for Hlth. Sci., Tulsa, OK

Abstract: Unregulated use of opioids such as heroin has escalated into a public health emergency. Heroin use disorder is a life-long affliction manifested by persistent heroin-seeking behavior during abstinence, eventually leading to relapse. Using our recently developed TUBE-mass spectrometry approach we found that males had a higher loss, while females had a higher gain of M1 polyubiquitination mark on target proteins in the nucleus accumbens (NAc) at early abstinence (abstinence day-AD1) following heroin self-administration, which coincidentally correlates with higher self-administration of heroin in females. In both sexes, a large set of proteins predominantly found in astrocytes and/or neurons had significantly altered M1 polyubiquitination at AD1, though, surprisingly, these proteins differed significantly between sexes. Further, a cell-type independent CRISPR-dCas9-mediated knockdown of the *Rnf31* enzyme that mediates M1 polyubiquitination resulted in attenuation of cue-induced seeking in males at AD1 that continued at AD14 while potentiating the behavior in females at only AD14. This is the first evidence that M1 polyubiquitination may be involved in neurobehavioral adaptation in the NAc in a sex-specific manner following volitional heroin administration, which contributes to cue-induced heroin seeking at protracted abstinence.

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Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.17/M13

Topic: G.09. Drugs of Abuse and Addiction

Title: Heroin self-administration induces sex-specific SUMOylation at early abstinence.

Authors: *S. CHAKRABORTY[1], N. PREVEZA[2], A. JEFFERS[1], T. J. JAROME[2], S. MITRA[3];
[1]Oklahoma State Univ. Ctr. for Hlth. Sci., Tulsa, OK; [2]Virginia Technol., Blacksburg, VA; [3]Pharmacol. and Physiol., Oklahoma State Univ. Ctr. for Hlth. Sci., Tulsa, OK

Abstract: Heroin use disorder is a life-long affliction manifested by profound withdrawal syndrome and high relapse rates. While gene expression and translational mechanisms have been extensively studied in postmortem brain samples and preclinical models, post-translational modifications (PTMs) have received less attention. Unbiased genetic analysis firmly implicates PTMs in the etiology of several psychiatric disorders, warranting further examination of the role of these PTMs underlying disease states. SUMOylation is an evolutionarily conserved PTM mechanism whereby, a small protein comprised of ~100 amino acids called Small Ubiquitin-like Modifiers (SUMO) is covalently attached to lysine residues of proteins. Using our recently

developed novel SUMO Capture Assay coupled with liquid chromatography-mass spectrometry, we identified sex-specific SUMOylation on protein targets at early abstinence without changes to global SUMOylation levels. This is the first evidence of SUMOylation being altered due to contingent heroin administration that might underlie long-term neuroadaptations.

Disclosures: S. Chakraborty: None. **N. Preveza:** None. **A. Jeffers:** None. **T.J. Jarome:** None. **S. Mitra:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.18/M14

Topic: G.09. Drugs of Abuse and Addiction

Title: Behavioral predictors of drug-seeking across the incubation of craving

Authors: *N. RUIZ[1], H. MAYBERRY[1], C. DRESSLER[2], C. PAPAZIAN[1], M. MCCORMICK[1], S. YOON[1], V. P. MURTY[2], M. E. WIMMER[2];
[1]Temple Univ., Philadelphia, PA; [2]Psychology, Temple Univ., Philadelphia, PA

Abstract: The incubation of craving is a phenomena where craving for a drug or reward increases over extended periods of abstinence. It is well established that cue-induced craving leads to relapse in individuals living with substance use disorders. Measuring craving has been made possible by animal models of incubation, which rely on rodents performing instrumental behaviors to self-administer drugs. Reward seeking is later measured by the amount of instrumental actions the animals will perform in absence of drug reinforcement. Quantifying the instrumental behaviors performed in response to drug-related cues has been the gold standard of measuring craving in animals, but craving and relapse encompass a suite of different behaviors reflecting different affective/cognitive processes. Historically, stereotypic behaviors such as locomotion, grooming, and sniffing have been associated with addiction-like traits in rodents. Previous work found these behaviors display unique profiles alongside the incubation of craving for both drug and nondrug rewards over periods of abstinence. However, how these behaviors predict lever pressing over time has not been explored. This project re-analyzed a dataset of male and female rats who underwent 10d of either intravenous opioid or oral sucrose self-administration. Cue-induced seeking tests were conducted after 1 or 30d of forced abstinence, which were recorded and scored instances of locomotion, sniffing, and grooming. Using a hierarchical modeling approach, we show that locomotion and grooming were predictive of lever-pressing behaviors to reward cues (p's < 0.001). These behaviors differentially predicted lever pressing as a function of abstinence, wherein locomotion was more predictive of lever pressing early during abstinence ($p < 0.001$) while sniffing and grooming were more predictive of lever pressing after extended periods of abstinence ($p < 0.001$). These findings present the foundation of understanding the inter-relationship between different drug-seeking behaviors.

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Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.19/M15

Topic: G.09. Drugs of Abuse and Addiction

Support: Discovery Grant from Natural Sciences and Engineering Research Council of Canada

Title: Consolidationofappetitiveassociative learning: modulation by an opioid agonist

Authors: *B. GINSON[1], G. GRANDISON[1], F. LERI[2];
[2]Psychology, [1]Univ. of Guelph, Guelph, ON, Canada

Abstract: Although the opioid system is involved in memory consolidation, there are learning, motivational and pharmacological factors that determine the effects of post-training administration of opiates.To explore these factors, male Sprague-Dawley rats received 1 mg/kg heroin immediately following eight sessions (4 pairings of vehicle & drug) of place conditioning induced by injections of the same heroin dose. In addition to a second group injected with vehicle post-conditioning, a third group received 3 mg/kg naloxone (a non-selective opioid antagonists) following post-conditioning heroin to block its potential effect on consolidation of place conditioning memory. Immediately after all post-conditioning injections, rats were placed in monitoring chambers for 60 min to measure locomotion and behavioral signs of heroin withdrawal. Place preference was assessed after 1 pairing (CPP Test 1) and again after 3 additional pairings (CPP Test 2). On CPP Test 1, there was a significant preference only in the group injected with 1 mg/kg heroin post-conditioning. However, on CPP Test 2, only animals injected with vehicle and with 1 mg/kg heroin + 3 mg/kg naloxone post-conditioning displayed significant preferences. The analysis of behaviors displayed in the post-conditioning monitoring chambers suggested possible pharmacological mechanisms to interpret these place preference results. In fact, relative to the animals injected with vehicle, those injected with 1 mg/kg heroin post-conditioning displayed a catatonic state which showed recovery over repeated injections. This suggests that post-conditioning heroin may have enhanced consolidation of place conditioning memory initially, but then caused tolerance to its own rewarding effects, leading to essential extinction of the learned association as a result of additional pairings.Interestingly, a different pharmacological process occurred in animals injected post-conditioning with 1 mg/kg heroin + 3 mg/kg naloxone. In fact, relative to animals injected with vehicle, they displayed progressively lower motor activity and well as a progressive increase of wet-dog shakes over successive injections. Thus, in this group, the observation of a CPP by Test 2 is consistent with our previous demonstrations of withdrawal-induced facilitation of object memory consolidation.Taken together, these data suggest the intriguing possibility that activation of

opioid receptors post-training can impact the process of memory consolidation as well as alter the effects of the unconditioned stimulus (in this case heroin) employed during conditioning.

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Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.20/M16

Topic: G.09. Drugs of Abuse and Addiction

Support: Mellon Foundation Funding to ALR
Summer Research Award American University to SH

Title: Interoceptive stimulus control is associated with the rate of acquiring morphine self-administration

Authors: *S. HUANG, A. L. RILEY;
Neurosci., American Univ., Washington, DC

Abstract: Interoceptive stimulus control is associated with the rate of acquiring morphine self-administration
Huang, Shihui; Riley, Anthony L.Department of Neuroscience, American University, Washington, D.C. USA.
Background. Clinical research has linked individual variability of interoception to differential susceptibility for dysregulated drug use, yet it remains unclear how interoceptive information helps regulate intake. Using a conditioned taste avoidance drug discrimination learning (CTA/DDL) task, we have demonstrated that a morphine-induced state can signal an impending aversive effect associated with saccharin, thus setting the occasion for avoidance. Here, we examined whether the variability in acquiring this interceptive stimulus control correlates with differences in morphine self-administration. **Methods**. In 24 male Sprague-Dawley rats, individual variability was assessed in the CTA/DDL task with morphine (10 mg/kg, IP) as the interoceptive signal. Rats within the lower and upper 50% of the ranking score were designated as weak- and strong-interoceptive-control subjects (WIC and SIC) and underwent IV self-administration to assess the acquisition, escalation, and persistence of morphine intake. **Results**. 30% of rats failed to acquire interoceptive stimulus control, consuming comparable levels of saccharin on both morphine and vehicle sessions, while 40% of rats acquired strong control, consuming at least 30% less saccharin on morphine relative to vehicle sessions. SIC rats learned to self-administer morphine more rapidly under the 2-hr access (FR1). Although other behavioral endpoints did not reach statistical significance, SIC rats displayed a greater level of active lever-pressing during 4-hr and 6-hr access (FR1), while WIC rats displayed higher breakpoints under progressive ratio assessments. **Conclusions**. These data suggest that rats more efficient in using interoceptive drug states to avoid aversive effects are more sensitive to the reinforcing effects of

the drug, as evidenced by the more rapid acquisition of morphine self-administration. Although statistically nonsignificant, these rats also showed less persistent motivation for the drug when faced with increasing cost. It remains to be explored whether WIC and SIC would exhibit different behavior under intermittent access, extinction, and reinstatement.

Disclosures: S. Huang: None. **A.L. Riley:** None.

Poster

PSTR040: Opioids: Reinforcement, Seeking and Reinstatement

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.21/M17

Topic: G.09. Drugs of Abuse and Addiction

Support: CIHR PJT-186231

Title: The effects of increased heroin availability on punishment-induced abstinence and stress-induced relapse in rats

Authors: *E. PAGE[1], A. PAWLAK[4], D. MORALES[2], C. BORGES[1], E. G. AH-YEN[1], S. DORRANCE[2], U. SHALEV[3];
[1]Concordia Univ., Montreal, QC, Canada; [2]Concordia Univ., Montréal, QC, Canada; [3]Dept. of Psychology, Concordia Univ., Montreal, QC, Canada; [4]Concordia University, Montreal, Montreal, QC, Canada

Abstract: Relapse to substance use is a critical obstacle for effective treatment, and stress is a one of the major triggers for relapse. We have previously shown that acute food deprivation stress robustly reinstates extinguished drug seeking in animal models. In addition, patterns of drug intake have a strong impact on drug intake and motivation for drug seeking. In the current study we assessed the effect of a continuous 5-minute drug access under a seeking-taking chain schedule on the development of punishment-imposed abstinence and acute food deprivation-induced relapse. Ten female and ten male Long-Evan rats were trained to self-administer heroin (0.05 mg/kg/infusion). Next, punishment-induced abstinence was achieved by probabilistic exposure to electric foot-shock following completed seek cycles. Two subsequent relapse tests were conducted under sated or food-deprived conditions. Preliminary results show that food deprivation led to a robust increase in drug seeking in both males and females. In addition, females showed greater resistance to punishment than males. This provides evidence that extended access, which more closely mimics the human condition, intensifies stress-induced relapse. In future experiments, we will investigate the brain circuits that are involved in the effect of environmental challenges on drug seeking and taking.

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Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: G.09. Drugs of Abuse and Addiction

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H2020 - H2020-WIDESPREAD-05-2017-Twinning (EpiEpinet) under grant agreement No. 952455
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Title: Good times, bad times: unraveling the role of sex and stress in the acute and post-acute actions of psilocybin

Authors: *M. FARINHA-FERREIRA[1,2,3], C. MIRANDA-LOURENÇO[1,2], C. GALIPEAU[1,2], Z. LENKEI[3], A. M. SEBASTIAO[1,2];
[1]Inst. de Farmacologia e Neurociências, Faculdade de Medicina, Univ. de Lisboa, Lisboa, Portugal; [2]Inst. de Medicina Mol. João Lobo Antunes, Faculdade de Medicina, Univ. de Lisboa, Lisboa, Portugal; [3]Univ. Paris Cité, Inst. of Psychiatry and Neurosci. of Paris (IPNP), INSERM U1266, Paris, France

Abstract: Recently, there has been an upsurge of interest in psilocybin as a potential breakthrough therapy for multiple difficult-to-treat psychiatric disorders. Despite this, several significant questions remain unaddressed. For one, little research has been done regarding the role of sex as a biological variable in psilocybin effects. Furthermore, there has yet been no research into the role played by the quality of the environmental context during acute effects, on the post-acute mood-altering actions of psilocybin. To address these questions, we performed a series of studies using adult male and female C57BL6/J mice.
First, we tested if acute psilocybin effects differ as a function of sex. For this, mice were injected with either saline or psilocybin (5mg/kg; i.p.) and observed for 30min to quantify head-twitch response (HTR) frequency. Notably, while psilocybin increased HTR frequency in both sexes, a greater effect was observed for females, suggesting a difference in sensitivity to the acute effects of psilocybin.
Secondly, we tested if concomitant stress exposure during acute drug effects impacted the post-acute actions of psilocybin. For this, mice were injected with saline or psilocybin, and returned to their home cage or exposed to restraint stress (RS) for 60min. Anxiety- and depressive-like behaviors were assessed starting 24h following drug administration, using the marble burying (MBT), novelty-suppressed feeding (NSFT), and splash tests (ST). Psilocybin induced significant anxiolytic-, but not antidepressant-like, effects in both sexes. Interestingly, while concomitant RS exposure effectively blocked psilocybin-induced anxiolytic-like effects in the MBT for both sexes, in the NSFT it only did so for males.
Lastly, we assessed if RS during psilocybin effects modulated biological markers of stress. For this, mice were treated as in the previous study, and sacrificed after 60min to assess plasma corticosterone levels, using ELISA. While both RS and psilocybin independently increased the

levels of plasma corticosterone, no additive or interactive effects were observed for either sex. Overall, data suggests that psilocybin might have a greater impact in females, the mechanisms of which remain undetermined. Furthermore, data suggests the quality of context in which acute psilocybin effects are experienced may influence the post-acute mood-altering effects. Lastly, this contextual dependence of psilocybin effects appears to differ between sexes. These findings have significant relevance for the therapeutic, but also recreational, use of psychedelics.

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Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR041.02/M19

Topic: G.09. Drugs of Abuse and Addiction

Support: European Union (EU) Home Affairs Funds, NextGenPS project (number: 101045825)
Ministerio de Ciencia e Innovación (PID2022-137541OB-I00)

Title: The psychedelic 25C-NBF promotes neural plasticity and has fast-acting antidepressant properties

Authors: *N. NADAL-GRATACOS[1,2,3], N. WEISS[1], C. RIERA COLOMER[1], B. FUMÀS[1], J. MARGALL[1], M. H. BUENROSTRO-JAUREGUI[4], X. BERZOSA[5], D. PUBILL[1], J. CAMARASA[1], E. ESCUBEDO[1], R. LÓPEZ-ARNAU[1];
[1]Dept. of Pharmacol., Toxicology and Therapeut. Chem., Univ. de Barcelona, Barcelona, Spain; [2]IQS School of Engineering, Universitat Ramon Llull, Barcelona, Spain; [3]Department of Psychology, Universidad Iberoamericana, Mexico City, Mexico; [4]Dept. of Psychology, Univ. Iberoamericana, Mexico City, Mexico; [5]IQS Sch. of Engin., Univ. Ramon Llull, Barcelona, Spain

Abstract: In the last decades, there has been a rapid emergence and propagation of new psychoactive substances (NPS), with several psychedelics gaining significant attention from researchers due to their therapeutic potential for the treatment of several neuropsychiatric disorders. In this study, we focused on the phenethylamine 25C-NBF, a novel psychedelic compound that has received limited attention to date. Thus, the aim of this study was to investigate the hallucinogenic profile of 25C-NBF, as well as its ability to promote neural plasticity and antidepressant properties in mice. For this purpose, male Swiss CD-1 mice (6-11 weeks old) have been used for the behavioral studies. The hallucinogenic effects were studied with the head twitch response (HTR), a fast side-to-side rotational head movement that occurs after activation of the 5-HT_{2A} receptor in rodents. Administration of 25C-NBF produced a dose-dependent increase in HTR ($n=12$, $p < 0.001$). Then, the antidepressant effects of 25C-NBF were

tested using the tail suspension test (TST) and the sucrose preference test (SPT). For both experiments, mice were subjected to 21 days of corticosterone (40 mg/kg) administration to induce stress. On day 22, a 10 mg/kg dose of 25C-NBF was administered. Our results showed a significant antidepressant effect of a single dose of 25C-NBF 24h after injection (TST: n=18; $p < 0.05$; SPT: n=12; Stress $p < 0.001$, Treatment $p > 0.05$, Stress x Treatment $p < 0.05$). Several authors have suggested that the therapeutic effects of psychedelics are due to their potential to induce neural plasticity. Therefore, the effects of a 10 mg/kg dose of 25C-NBF on spinogenesis in the PFC was assessed using Golgi-Cox staining. Our results demonstrated an increase of dendritic spines both in the anterior cingulate cortex (ACC) and in the prelimbic cortex (PL) 24h post-administration (n=6; $p<0.05$). To sum up, 25C-NBF induces HTR and acts as a fast-acting antidepressant in mice, which could be explained by its ability to promote neural plasticity in the PFC. This study offers value into the search of alternatives for treating individuals with treatment-resistant depression.

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Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

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Topic: G.09. Drugs of Abuse and Addiction

Support: Korea Brain Research Institute (KBRI, 24-BR-02-02 & 24-BR-04-04) basic science research program through the National Research Foundation of Korea (NRF, RS-2023-00248148) funded by Ministry of Science and ICT

Title: Psilocybin administration increases c-Fos(+) cell density in the claustrum and cortex

Authors: *K. LEE[1], J. LEE[2], J. KIM[3], J. LEE[4], J. KIM[1];
[1]Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of; [2]Kyungpook Natl. Univ. Sch. of Med., Daegu, Korea, Republic of; [3]Daegu Univ., Daegu, Korea, Republic of; [4]Dankook Univ., Cheonan-si,, Korea, Republic of

Abstract: Psychedelics are a subclass of hallucinogenic drugs that primarily trigger non-ordinary mental states and an apparent expansion of consciousness. Recently, psychedelics, including psilocybin, MDMA, and LSD, have been reported to function as neurotherapeutics in psychiatric disorders. However, the underlying neural mechanisms are not yet well understood. A recent human fMRI study demonstrated that psilocybin acutely alters the activity of the claustrum, a brain structure located between the insular cortex and striatum. Since the claustrum is known to be reciprocally connected with the cortex, we hypothesized that psilocybin alters the

neuronal activity of both the claustrum and cortex. To investigate whether and how psilocybin administration alters neuronal activity, we injected psilocybin (1-3 mg/kg) into male and female mice and analyzed c-Fos activation in the structures. Our results revealed a significant increase in neuronal activation in the claustrum following psilocybin treatment in both sexes. However, cortical neurons showed differences in c-Fos cell density in a cortical area-specific manner. We further studied any difference in the psilocybin effects on parvalbumin and somatostatin interneurons, the two most common interneuron types in the cortex, by using cell type-specific markers. Those interneuron analysis also showed differences across different cortical areas we investigated. Anterior, but not posterior, cortical areas showed largely increased c-Fos cell density whereas posterior cortex showed increased activation in a subset of interneuron types. We also observed that neuronal activation across different cortical areas are slightly different between sexes. These results indicate that the effects of psilocybin are not universal across brain areas but regionally specific, cell type-specific, and sex-specifically different.

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Poster

PSTR041: Hallucinogens: Neural Mechanisms

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Topic: G.09. Drugs of Abuse and Addiction

Support: Templeton World Charity Foundation
Allen Institute
The Tiny Blue Dot Foundation

Title: Multiscale Electrophysiological Characterization of the Psychedelic State from EEG to Cortical and Thalamic Single Units in Head-fixed Mice

Authors: *Y. NAHAS[1], D. WYRICK[1], L. D. CLAAR[1], L. MARKS[1], P. SEYFOURIAN[1], S. RUSSO[2,1,3], C. KOCH[1], M. A. BUICE[1], I. REMBADO[1];
[1]Allen Inst., Seattle, WA; [2]Georgia Inst. of Technol. and Emory Univ., Atlanta, GA; [3]Univ. degli Studi di Milano, Milan, Italy

Abstract: The therapeutic potential of psychedelic drugs has recently surfaced in a wave of new clinical research investigating its effects as a treatment for neuropsychiatric disorders (Carhart-Harris and Goodwin, 2017). One example is the 5-HT agonist psilocybin, which successfully alleviated symptoms of major depressive disorders and addiction in humans (Raison et al., 2023; Johnson et al., 2017). Despite their promising results in clinical trials, the mechanisms underlying the effects of the psychedelic drugs remain unclear. To fill this gap, we characterize the markers of the psilocybin-induced psychedelic state using our unique experimental setup in head-fixed mice combining large-scale skull electroencephalography (EEG) with multiple Neuropixels 1.0 probes (each with 384 recording channels along a 10 mm long shaft; Jun et al.,

2017) while recording behavioral and physiological changes via running speed, pupil size, and respiration rate. The probes target both cortical and subcortical areas, allowing us to answer open questions about how the psychedelic drug modulates cortical and thalamic interactions (Kwan et al., 2022). Specifically, we assess how psilocybin affects temporal correlations between cortical and thalamic spike trains using a global synchrony algorithm (Li et al., 2007; Patel et al., 2012). These changes are then correlated to changes in the exponent of the aperiodic component (n in the 1/fn fit of the power spectrum in the linear scale, corresponding to the negative slope of the log-log power spectrum) and the periodic components (powers in different frequency bands) of the EEG frequency spectrum (Donoghue et al. , 2020). Notably, the use of whole-brain EEG recordings adds a translational attribute to the findings of the study. Preliminary analysis reveals that a decrease in running speed correlates with an increase in the exponent of the aperiodic component of the EEG frequency spectrum under both the psychedelic and non-psychedelic state. Overall, this study aims to build a multiscale and translational profile of the psychedelic state in the mouse. This effort will contribute to revealing the neural mechanisms underlying the acute effects of psilocybin that are potentially involved in alleviating symptoms of neuropsychiatric disorders in humans (Yaden D.B. and Griffiths R.R. 2021).

Disclosures: **Y. Nahas:** None. **D. Wyrick:** None. **L.D. Claar:** None. **L. Marks:** None. **P. Seyfourian:** None. **S. Russo:** F. Consulting Fees (e.g., advisory boards); Manava Plus. **C. Koch:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Intrinsic Powers. **M.A. Buice:** None. **I. Rembado:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.05/M22

Topic: G.09. Drugs of Abuse and Addiction

Support: National Institute of General Medical Science, R35GM152169

Title: Behavioral and genetic analysis of psychedelic drug action in C. elegans

Authors: *A. M. WHITE, A. D. BAUER, S. FAUMONT, S. R. LOCKERY;
Inst. of Neurosci., Univ. of Oregon, Eugene, OR

Abstract: The promise of psychedelic drugs as novel treatments for depression, post-traumatic stress disorder, and substance use disorder has fueled a "psychedelic renaissance" and renewed efforts to understand their behavioral effects and mechanisms of action. Psychedelics have particularly high affinity for serotonin 2A (5-HT2A) receptors, but the downstream signaling pathways that mediate their behavioral effects are mostly unknown. Delineation of these pathways is a critical need for the improvement of psychedelic treatments. *C. elegans* expresses six types of serotonin receptors. Two receptors (*mod-1*, *lgc-50*) are ion channels genetically unrelated to the mammalian ionotropic 5-HTR3 channel. The other four G-protein-coupled

receptors (*ser-1, ser-4, ser-5, ser-7*) are orthologs of five of the seven 5-HTR gene families expressed in humans; these *C. elegans* receptors couple to the same G-proteins as their mammalian orthologues indicating significant functional conservation. Here, we characterized the effects of the psychedelic drug 2,5-dimethoxy-4-iodoamphetamine (DOI) on three critical serotonin-regulated behaviors in *C. elegans*: feeding, egg-laying, and locomotion. We found that feeding rate (pharyngeal pumping frequency) was reduced by 60% in worms exposed to DOI. This effect is opposite to serotonin's effect on feeding but orthologous to psychedelic-induced hypophagia in mice. Pre-incubation with DOI (1 mM) had no effect on egg laying rate, whereas pre-incubation with serotonin at a standard dose (5 mg/mL) stimulated egg laying as expected. Finally, we observed dose-dependent effects of DOI on locomotion. At low doses (0.1-3.0 mM), DOI caused hyperactivity, in contrast to hypoactivity induced by serotonin. At a high dose (10 mM), DOI caused hypoactivity. The dose-dependent effects of DOI on locomotion mirror those in mice. Together, these data indicate that the psychedelic drug DOI is behaviorally active in *C. elegans*, a novel finding, and its effects on feeding and locomotion parallel those in rodents. Surprisingly, however, DOI's effects on all three behaviors are markedly distinct from those of serotonin in *C. elegans*. One possibility is that DOI has no effect (egg laying) or opposite effects (feeding, locomotion) on serotonin pathways; alternatively, it may activate pathways downstream of other receptors. Experiments to identify the receptors required for DOI's behavioral effects are underway.

Disclosures: A.M. White: None. **A.D. Bauer:** None. **S. Faumont:** None. **S.R. Lockery:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Oregon has filed a patent application on this technology.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.06/M23

Topic: G.09. Drugs of Abuse and Addiction

Support: NIMH Grant #5R01MH115020-03

Title: Longitudinal Effects of a Psychedelic Compound on Neurological Mechanisms and Compulsive Behavior in Mice

Authors: *J. REDMOND, Y. JAQUES, M. KO, D. KAUFER;
Univ. of California, Berkeley, Berkeley, CA

Abstract: Compulsivity is the urge to perform repetitive and consistent behaviors excessively. These behaviors are commonly associated with stress disorders such as post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD). Recent clinical research has highlighted the potential for psychedelics such as psilocybin and MDMA to be used as

therapeutics for PTSD. Yet, it is unclear to what extent psychedelics can help reduce compulsive behaviors and how long the effects may persist after a single initial exposure. Prior experiments in our lab have shown decreases in compulsive behavior ~3 hours after a single 2,5-Dimethoxy-4-iodoamphetamine (DOI) intra-peritoneal injection of 3 mg/kg in mice. Thus, the goal of the present study is to examine the duration of the therapeutic effects of psychedelics in compulsive behaviors using mice. Our time series experiment used thirty 8-10-week-old male mice, tested at -1, 0, 1, and 7 days. We hypothesize that DOI, a synthetic psychedelic, will show decreases in compulsive behavior until day 7. On each test day, mice were placed into the nestlet shred test (NST), and marble burying (MB) test to measure compulsive behavior. Mice were injected with saline or the highest dosage of DOI at 3 mg/kg on day 0 only. Immediately following injection on day 0, mice were video recorded for ~10 minutes for head twitch behavior. Head twitch is a commonly reported effect of psychedelic drug exposure in rodents. Preliminary data shows significant decreases in nestlet shredding and marble burying on day 0, as previously demonstrated. On day 1, only the MB test showed reduction of compulsive behaviors in the DOI group. Lastly, on day 7 we found that nestlet shredding behavior increases, and there are no significant differences between groups in the MB test. Less nestlet shredding and marble burying can be interpreted as an absence or reduction in compulsive behavior. In summary, we found a unique bifurcating effect of DOI in compulsive behaviors during our longitudinal examination of the drug. This new finding will help clinical application of psychedelics by increasing understanding of potential long-term effects on behavioral phenotypes beyond the time of psychedelic exposure. Following the aforementioned behavioral assays, brain tissue was collected and cryosectioned to isolate regions of interest. Using these brain samples, our ongoing experiments using immunohistochemistry aim to address the effects of DOI on myelin plasticity in the prefrontal cortex, striatum, and hippocampus regions of the brain. These results may provide insight to the duration and extent of the plastic changes seen in these regions following psychedelic exposure.

Disclosures: **J. Redmond:** None. **Y. Jaques:** None. **M. Ko:** None. **D. Kaufer:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.07/M24

Topic: G.09. Drugs of Abuse and Addiction

Title: The non-hallucinogenic serotonin 1B receptor is involved in the persisting behavioral effects and neural mechanisms of psilocybin in mice

Authors: *S. FLEURY[1], K. M. NAUTIYAL[2];
[1]Psychological and Brain Sci., Darmouth Col., Hanover, NH; [2]Neurosci., Dartmouth Col., Hanover, NH

Abstract: Recent studies have demonstrated the strong potential of psychedelic therapies for the treatment of psychiatric disorders, and there are currently many ongoing clinical trials aimed at investigating the effect of psilocybin on major depressive disorder. The persisting clinical effects of psychedelic therapies are most commonly attributed to activation of the serotonin 2A receptor (5-HT2A R) based on its role in the acute hallucinatory effects. However, psilocin, the active metabolite of psilocybin, binds to many serotonin subtypes. Recent studies in rodents suggest some therapeutic effects may be independent of the 5-HT2AR. Investigating the role of other 5-HTRs is crucial to comprehend psilocybin's lasting clinical effects. We hypothesize that psilocybin may influence depressive-like behaviors via 5-HT1BRs, a non-hallucinatory subtype of serotonin receptors previously implicated in mediating depressive phenotypes and neural plasticity. We first established a protocol to test psilocybin's effects on anxiety-like behavior, anhedonia, and cognitive flexibility in mice. Our results show that psilocybin reduced anxiety and decreased anhedonia in female mice treated with chronic corticosterone. Next, we assessed the role of 5-HT1BR in mediating these behavioral responses using loss-of-function mouse models. Interestingly, female mice lacking 5-HT1B lacked the behavioral changes seen following psilocybin injection in control mice. Specifically, psilocybin-treated female knockout mice showed no significant reversal in cort-induced anhedonia, no increased exploration in the elevated plus maze, and no decreased anxiety in the novelty-suppressed feeding test compared to saline-treated knockout mice. We then used c-fos labeling to quantify whole-brain neural activity following psilocybin administration in controls and mice lacking 5-HT1BR to compare neural activity and assess functional connectivity across specific brain regions. Whole brain c-fos analysis shows that 5-HT1BR expression influences brain-wide activity following psilocybin administration in regions regulating emotional processing and cognitive function, such as the amygdala and basal ganglia. Current work is aimed at quantifying perineuronal nets (PNNs) following psilocybin administration as a measure of plasticity. Overall, this research suggests that psilocybin induces antidepressant effects at high doses in female mice administered corticosterone, which may be partially modulated by the activation of the non-hallucinatory serotonin 1B receptor.

Disclosures: S. Fleury: None. **K.M. Nautiyal:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.08/M25

Topic: G.09. Drugs of Abuse and Addiction

Support: ANID 212208073
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DICYT-USACH 022343RM
FONDECYT 1161524
DICYT-USACH 021843MM

FONDECYT 11140430
DICYT-USACH 0211843RS

Title: Non-hallucinogenic psychedelics derivatives from n,n-dimethiltryptamine (dmt) restores hippocampal synaptic plasticity in the learned helplessness mice model used for the study of depression.

Authors: *F. E. GODOY[1], J. ROJAS-BURGOS[2], B. CASSELS[2], B. E. MORALES[1], P. ROJAS[1], C. A. ROZAS[1];
[1]Biología, Univ. de Santiago de Chile, Santiago, Chile; [2]Química, Univ. de Chile, Santiago, Chile

Abstract: The major depressive disorder it's a member of the mood disorders, affecting nearly 300 million people worldwide, and with a high prevalence on adolescents and young adults. Several animal models have been developed like the learned helplessness model (LH) in which it has been described diminished hippocampal volume, decreased density of dendritic spines, changes on levels of neurotrophic factors like BDNF and the expression of glutamate receptors. On the last decade the psychedelic research and use has regained interest for their capabilities to enhance synaptic plasticity and generate fast antidepressive effects after few doses. Nevertheless, the exposure of patients to hallucinogenic agents could be a therapeutical issue. Several psychedelic derivatives like isoDMT, 5-MeoisoDMT, and 6-MeoisoDMT that doesn't have the hallucinogenic effect when tested on animal models have been synthesized recently, so we asked if these non-hallucinogenic derivatives could generate the recovery of the synaptic impairment present on the LH mice model and replicate the antidepressant properties of other hallucinogenic psychedelics. To determine changes on *ex vivo* hippocampal synaptic plasticity of LH mice we measured fEPSP recordings and LTP induction on CA3-CA1. We used the open field to test anxiety and hyperlocomotion, Y maze for spatial referential memory and forced swim. The drugs were delivered *ex vivo* directly over the hippocampal slices (on concentrations ranging from 0.5 to 50 µM). We have found that the LH mice presents a decrease on the active mobility time in the forced swim test (control 176.8±12.4s, n 5; LH 88.3±7.4s, n 16; $p<0.005$) and anhedonia (control 80.2±10.6%, n 4; LH 68.1±7.7%, n 12, $p>0.005$). LH mice display an impairment on hippocampal plasticity (control 152.1±3.5%, n 13; LH 122.1±2.63%, n 19, $p<0.0001$) evaluated after theta burst stimulation (TBS).This impairment persists 10 days after the last exposure to unpredictable stress. The impaired LTP on LH mice is restored to values like control mice (control 154.8±7.4%, n 5; LH+IsoDMT 147.2± 6.44%, n 8; LH+5-MeoisoDMT 159±3.5, n 6; LH+6-MeoisoDMT 144.7±6.7, n 7; $p>0.005$) by the application in bath of 10 µM of isoDMT, 5-MeoisoDMT and 6-MeoisoDMT. In conclusion, these results suggest that LH mice exposed to unpredictable stress present behavioral alterations and impairment oh hippocampal glutamatergic neurotransmission and plasticity, and that the acute exposure to this DMT derivatives can regulate the LTP impairment, recovering it to levels like the control animals. More evidence its needed to dilucidated the mechanisms by which they exert their effects.

Disclosures: F.E. Godoy: None. **J. Rojas-Burgos:** None. **B. Cassels:** None. **B.E. Morales:** None. **P. Rojas:** None. **C.A. Rozas:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.09/M26

Topic: G.09. Drugs of Abuse and Addiction

Title: The effect of psychedelic derivatives on cocaine- and fentanyl-seeking in mice

Authors: *T. LOVELL[1], A.-C. BOBADILLA[2];
[2]Biomed. Sci., [1]Colorado State Univ., Fort Collins, CO

Abstract: The effect of psychedelic derivatives on cocaine- and fentanyl-seeking in mice
The re-emergence of research into psychedelic compounds has shown promising therapeutic benefits for a wide variety of human health disorders, including substance use disorders (SUD). Substances of abuse hijack the reward system of the brain, leading to repeated and maladaptive drug use, despite detrimental impacts on mental and physical well-being. A prominent component of SUD is context-induced relapse, wherein the context surrounding drug use is associated with rewarding effects, and re-exposure to the context can trigger cravings and drug seeking. Utilizing the Conditioned Place Preference (CPP) paradigm of associative learning, we explored reward-seeking behavior in wild-type C57BL/6J mice. This model includes eight days of 15-minute conditioning sessions, during which subjects are trained to pair a contextual compartment with receiving intraperitoneal injections of a rewarding drug (cocaine or fentanyl) and another context with receiving a saline vehicle. On the ninth day, subjects are administered a psilocybin derivative and tested for which contextual compartment they prefer, measured as the percentage of time spent in the drug-paired compartment. We tested various doses of psilocybin derivatives for their impact on preference for cocaine-paired and fentanyl-paired contexts in males and females. Additionally, we assessed the potential anxiolytic and anxiogenic properties of each compound with elevated plus maze and open field models of anxiety testing to characterize adverse side effects. Finally, we performed whole-brain clearing and 3D-mapping of transgenic Ai14xcFos-TRAP2 mouse brains to image and compare psychedelic-linked fluorescence-labeled populations of cells across brain regions. Implications from this investigation may reveal psychedelic compounds, specifically psilocybin and its derivatives, as competitive performers in reducing drug-seeking in rodents.

Disclosures: **T. Lovell:** None. **A. Bobadilla:** 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.; CaaMTech Inc..

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.10/M27

Topic: G.09. Drugs of Abuse and Addiction

Support: Canada Research Chair
Canada Institutes of Health Research

Title: Psilocybin vs. lisuride: similarities and differences in their serotonergic, dopaminergic, sedative-, anxiogenic-, and antidepressant-like effects

Authors: *B. RICHARDSON[1], A. INSERRA[1], M. PILEGGI[1], T. PRUD'HOMME[1], D. WAN-YAN-CHAN[4], T. STRAND[5], M. LEYTON[2], N. SONENBERG[3], D. DE GREGORIO[6], J. S. SPROUSE[7], F. R. BAMBICO[4], G. GOBBI[1];
[1]Psychiatry, McGill Univ., Montreal, QC, Canada; [2]Dept Psychiatry, Psycholology, & Neurol., McGill Univ., Outremont, QC, Canada; [3]McGill Univ., Cote St-Luc, QC, Canada; [4]Psychology, Mem. Univ. of Newfoundland, St. John's, NL, Canada; [5]Psychology, Mem. Univ. of Newfoundland and Labrador, St. John's, NL, Canada; [6]Vita Salute San Raffaele Univ., Milan, Italy; [7]Diamond Therapeut. Inc, Stonington, CT

Abstract: Psychedelic drug-induced hallucinogenic and therapeutic effects are thought to reflect 5-HT2A receptor activation. Lisuride is a 5-HT2A receptor agonist and structural analog of LSD but it does not produce hallucinogenic effects in humans. Given this, the present study compared effects of psilocybin and lisuride on behavior and both serotonin (5-HT) and dopamine cell firing within the dorsal raphe nucleus (DRN) and substantia nigra (SN), respectively, in adult male C57BL6/N mice (n = 5 - 15). Behavioral tests included the head twitch response (HTR), open field test (OFT), elevated plus maze (EPM), forced swim test (FST), and unconditioned burrowing response. HTR was scored during the first 10 minutes after acute intraperitoneal injections of psilocybin (0.3, 1 or 3 mg/kg), lisuride (0.05, 0.15 or 0.5 mg/kg), or vehicle. All other tests were conducted 20 min after injection. In vivo extracellular single-unit electrophysiology evaluated the effects of psilocybin (0.3, 1, 3 mg/kg) and lisuride (0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg) compared to vehicle, on 5-HT and dopamine neuronal firing activity. MDL100907 (0.2 mg/kg), a selective 5-HT2A antagonist, was used to block 5-HT effects of psilocybin and lisuride (n = 4 - 8). Psilocybin, but not lisuride, elicited the HTR ($p < 0.001$). Both psilocybin and lisuride decreased locomotion ($p < 0.001$) and elicited an anxiogenic-like effect ($p = 0.0031$), but at the lowest dose psilocybin also produced anxiolytic-like effects ($p = 0.0369$). Both lisuride ($p < 0.001$) and psilocybin ($p = 0.03$) decreased burrowing behavior. FST immobility was decreased by the highest dose of lisuride ($p = 0.0051$), but not by psilocybin. 5-HT cell firing was decreased by both psilocybin ($p = 0.0052$) and lisuride ($p = 0.0011$) but only psilocybin's effect was prevented by MDL100907. Dopamine neuron firing was decreased by psilocybin at 2 mg/kg ($p = 0.0067$, -68%) and 3 mg/kg ($p = 0.0018$, -79%), but only by the highest dose of lisuride (0.5mg/kg; $p = 0.0449$, -59%). Together, these results suggest that HTR and SN dopamine neuron firing changes are induced more robustly by psilocybin than lisuride. Both drugs decrease 5-HT cell firing but only psilocybin's effect was 5-HT2A mediated, only psilocybin produced an anxiolytic-like effect, and only lisuride yielded an antidepressant-like effect. Further research is ongoing to better understand the intrinsic activity of these compounds on 5-HT and DA sub-receptors in different areas.

Disclosures: B. richardson: None. **A. Inserra:** None. **M. Pileggi:** None. **T. Prud'homme:** None. **D. Wan-Yan-Chan:** None. **T. Strand:** None. **M. Leyton:** None. **N. Sonenberg:** None. **D. De Gregorio:** 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.; Diamond Therapeutics Inc. **J.S. Sprouse:** A. Employment/Salary (full or part-time):; Diamond Therapeutics Inc. **F.R. Bambico:** None. **G. Gobbi:** 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.; Diamond Therapeutics Inc.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.11/M28

Topic: G.09. Drugs of Abuse and Addiction

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Universidad Austral, Proyectos categoria Trayectoria 2023
CONICET PIP 112202101 00198CO

Title: Serotonin receptor 2A deficiency alters thalamic gene expression induced by a single administration of the atypical psychedelic noribogaine in mice: evaluation of gender differences.

Authors: *M. VILLALBA[1], S. BOSCH[2], L. DI COSTANZO[3], B. GONZÁLEZ[4], J. GONZALEZ[4], P. D. TORTEROLO[5], I. CARRERA[4], F. J. URBANO[6], V. BISAGNO[3];
[1]Austral Univ., Derqui, Pilar., Argentina; [2]Austral Univ., Derqui, Pilar, Argentina; [3]Austral Univ., Pilar, Argentina; [4]Univ. de la Republica, Montevideo, Uruguay; [5]Schl Med., Montevideo, Uruguay; [6]IFIBYNE-CONICET, Buenos Aires, Argentina

Abstract: Changes in thalamocortical connectivity might be responsible for altered consciousness following psychedelic intake. Ibogaine, the main indole alkaloid isolated from the root bark of the African shrub Tabernanthe iboga, is an atypical psychedelic drug capable of inducing oneirogenic effects (waking dream-like states) and vivid memory recall. Ibogaine is metabolized mainly by CYP2D6 to the primary metabolite Noribogaine (Noribo). The main objective of this study was to analyze the contribution of the 5-HT2A receptor (5HT2AR) on the pharmacological effects of Noribo since it has been suggested that at least some of the effects of are linked to 5-HT2A activation and that it might also induce less cardiotoxicity, compared to ibogaine. We used the 5-HT2A receptor knockout (KO) (5-HT2A -/-) or wild type (WT), male and female mice. Mice were injected with a single Noribo dose (10 and 40 mg/kg), and qPCR

was performed on several genes including Calcium Voltage-Gated Channel genes in the Thalamus, CACNA1I (Calcium Voltage-Gated Channel Subunit Alpha1 I), CACNA1G (Calcium Voltage-Gated Channel Subunit Alpha1 G) and CACNA1a (P/Q-type voltage-dependent calcium channels). For male mice, we found that Noribo (10 mg/Kg; N10) increased CACNA1g, HCN2 and 5HT2AR expression only in WT mice, but no differences were found for KO. N10 increased CACNA1a mRNA in KO mice but not for WT and CACNA1i expression increased in both genotypes. For female mice, we found that N10 increased CACNA1i and CACNA1g expression only in KO mice, but no differences were found for KO. N10 increased CACNA1a mRNA in both genotypes and decreased HCN2 expression in WT and KO mice. We also used patch clamp recordings to characterize the effect of bath-applied Noribo; 50 mM on intrinsic and synaptic responses from thalamocortical slices from male WT and 5-HT2A KO. We observed (in current clamp) a reduction in Cav3.1, T-type mediated low threshold spike amplitude in ventrobasal (VB) neurons. For voltage-clamp, we observed significantly less current density of T-type currents in VB neurons from 5-HT2A KO ($p<0.05$). Noribo bath application reduced T-type current density in WT ($p<0.01$), but not from 5-HT2A KO. These results might indicate that Noribo can alter calcium channel physiology by blocking thalamocortical Cav3.1, T-type channels in the presence of 5-HT2A receptors. Additionally, we observed that Noribo changed thalamic gene the expression within the Thalamus a in a sexually dimorphic and genotype-dependent manner. Also, gene expression showed dose-dependency effects.

Disclosures: **M. Villalba:** None. **S. Bosch:** None. **L. Di Costanzo:** None. **B. González:** None. **J. Gonzalez:** None. **P.D. Torterolo:** None. **I. Carrera:** None. **F.J. Urbano:** None. **V. Bisagno:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.12/M29

Topic: G.09. Drugs of Abuse and Addiction

Support: R00 DA048119

Title: Whole-brain effects of psychedelics on stress-cued and heroin seeking behaviors

Authors: *M. J. FRANCIS[1], A. C. W. SMITH[2];
[1]Neurosci., Med. Univ. of South Carolina Neurosci. Grad. Program, Charleston, SC; [2]Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Opioid use disorder (OUD) and Post-Traumatic Stress Disorder (PTSD) are highly comorbid and mutually exacerbating. There is a critical unmet need for pharmacotherapeutics targeting stress-precipitated relapse, as stress-conditioned stimuli are a major driver of relapse in comorbid patients. Psychedelic drugs like psilocybin show promise in the treatment of

neuropsychiatric disorders including substance use disorders and PTSD. Despite ongoing clinical trials investigating psilocybin for OUD, there is a critical gap in the preclinical profiling of psychedelics in OUD models. We examined the behavioral and neural effects of psychedelics on stress-cued reinstatement of heroin seeking in mice (C57BL/6, n=36). Mice underwent restraint stress in the presence of an odor that became a stress-conditioned stimulus (CS). They were then trained to self-administer (SA) heroin in the presence of discrete light/tone cues (heroin-CS). Following 14 days of heroin SA, mice began 14 days of extinction training, where nose-pokes had no programmed consequences. We administered 1 mg/kg 2,5-dimethoxy-4-iodoamphetamine (DOI), psilocybin, or vehicle immediately following three extinction sessions. Reinstatement of drug seeking was elicited by both stress-CS and heroin-CS. Psilocybin and DOI each attenuated stress-cued reinstatement. Whole-brain c-Fos mapping was used to identify structures that are differentially activated by stress-cued reinstatement in psychedelic- vs. vehicle-treated mice. Additionally, we mapped c-Fos expression in response to acute treatment with DOI (n=18). Finally, FosTRAP-tdTomato mice were used to double-label neuronal ensembles activated by both acute restraint stress and re-exposure to stress-CS (n=12). These experiments identified the anterior insular cortex (aIC) as a brain structure that may mediate the interaction between psychedelics, stress, and OUD. Stress-cued reinstatement increased c-Fos expression in the aIC in vehicle but not DOI-treated mice. Additionally, acute DOI injection increased c-Fos in the aIC relative to vehicle controls. Finally, we identified an aIC ensemble that is activated by both acute restraint stress and re-exposure to stress-CS. Ongoing experiments include activity-dependent anterograde tracing from psychedelic-responsive projections from the aIC to identify circuits mediating the effect of psychedelics, and further analysis of the interaction between psilocybin and stress on global c-Fos expression. This research contributes to the understanding of stress-precipitated reinstatement and may help to elucidate novel targets for the treatment of addiction and stress disorders.

Disclosures: **M.J. Francis:** None. **A.C.W. Smith:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

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Topic: G.09. Drugs of Abuse and Addiction

Support: Tiny Blue Dot Foundation

Title: Brain-wide Survey of Mouse Transcriptomic Cell Types Activated by Acute Psilocybin Injection

Authors: *S. VARGAS[1], D.-W. KIM[2], R. CHAKRABARTY[3], J. GOLDY[4], A. CHAKKA[3], N. DEE[2], T. CASPER[2], B. NGUY[3], J. GUZMAN[3], M. TIEU[2], K. JAMES[3], D. BERTAGNOLLI[3], A. TORKELSON[3], Z. YAO[2], C. LEE[5], K. SMITH[3], J. T. TING[6], H. ZENG[2], C. KOCH[2]; [1]Brain Sci., Allen Inst., seattle, WA; [2]Allen Inst. for Brain Sci., Seattle, WA; [3]Allen Inst., Seattle,

WA; [4]BiCore, Allen Inst. For Brain Sci., Seattle, WA; [5]Modeling Analysis and Theory, Allen Inst. For Brain Sci., Seattle, WA; [6]Human Cell Types, Allen Inst. For Brain Sci., Seattle, WA

Abstract: Classical psychedelics, known as serotonergic hallucinogens, have shown therapeutic potential to treat a wide range of psychiatric disorders in recent early-stage clinical trials. However, due to limited research systematically investigating the neural substrates of psychedelic effects, the underlying mechanisms of psychedelic brain action remain elusive except for the necessary involvement of the G-protein-coupled 5-HT 2A receptors. The *Allen Institute for Brain Science* (AIBS) is at the forefront of characterizing molecular and anatomical cell types in mammalian brains. Recently, AIBS released a comprehensive whole-mouse brain cell type atlas, the *Allen Brain Cell* (ABC) atlas and introduced a variant of single-cell RNA sequencing (scRNA-seq) technology, called "Act-seq", to identify transcriptomic cell types (t-types) selectively active during a particular behavior or manipulation. Act-seq measures endogenously induced expression of >100 immediate early genes (IEGs), while unwanted IEG activation during sample preparation is minimized. We performed large-scale (~20 brain areas for both sexes) Act-seq experiments after in-vivo administration of psilocybin (1mg/kg; intraperitoneally) to mice. After stringent data QC, we collected 218,086 neurons from 116 10x v3.1 Act-seq libraries. Following the mapping of Act-seq data onto the ABC atlas, we identified neuronal t-types showing increased or decreased IEG expression after acute psilocybin injection compared to control (saline) in each sex. Overall, we found remarkably few excitatory or inhibitory t-types with increased IEG expression in cortex, with more t-types showing significantly decreased IEG expression. Some brain areas such as VISp, RSP, PL-ILA-ORB and claustrum had a notable absence of t-types exhibiting any increase in IEG expression. Our Act-seq data also revealed region-specific IEG induction in AUD, PL-ILA-ORB, LSX, HY: MEZ-PVZ-PVR, PAL, PONS: Pmot-Psat, PAR-POST-PRE-SUB-ProS and reductions (e.g. ACA, VISp) in subsets of t-types. We also discovered sexually dimorphic IEG activation patterns in some brain regions. For example, "STR D1 Gaba_2" in STRv and "STR D2 Gaba_6" in STRd were activated by acute psilocybin only in male mice, whereas most activated t-types in LSX were found in female mice. To compare psylocibin Act-seq results with effects induced by other serotonergic psychedelics and to further investigate the mechanisms of psilocybin-induced cell-type activation, we will perform additional experiments, including in vivo administration of other psychedelic drugs, such as 5-MeO-DMT, and pre-treatment with ketanserin, a selective 5-HT_{2A} receptor antagonist.

Disclosures: S. vargas: None. **D. Kim:** None. **R. Chakrabarty:** None. **J. Goldy:** None. **A. Chakka:** None. **N. Dee:** None. **T. Casper:** None. **B. Nguy:** None. **J. Guzman:** None. **M. Tieu:** None. **K. James:** None. **D. Bertagnolli:** None. **A. Torkelson:** None. **Z. Yao:** None. **C. Lee:** None. **K. Smith:** None. **J.T. Ting:** None. **H. Zeng:** None. **C. Koch:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.14/M31

Topic: G.09. Drugs of Abuse and Addiction

Support: NSF GRFP
R01MH128217

Title: In vivo imaging of psychedelic actions on cerebral blood flow and neurovascular coupling

Authors: *R. T. ZIRKEL[1], C. LIAO[1], M. ISAACSON[1], D. A. RIVERA[2], M. YI[2], A. C. KWAN[2], N. NISHIMURA[2], C. B. SCHAFFER[2];
[2]Biomed. Engin., [1]Cornell Univ., Ithaca, NY

Abstract: The therapeutic potential of psychedelics for treatment of mood disorders has recently seen promising results. This has spurred many human neuroimaging studies to understand the mechanisms through which these therapeutic effects occur. These effects are attributed greatly to serotonin-receptor agonism, specifically the 2A receptor (5-HT2AR). Human neuroimaging studies have proposed significant functional reorganization of brain regions due to 5-HT2AR activation through blood-oxygen-level-dependent signals that infer brain activity. These results, however, have not considered the vasoactive effects that serotonin may play. Proper interpretation of these images requires the consideration of altered relations between neuronal activity and blood flow that could be linked to such receptor agonism. We assess neurovascular coupling (NVC) by recording micro- and mesoscale vascular changes in response to neuronal activity in the mouse visual cortex with the administration of psilocybin (a 5-HT2AR agonist). We perform two-photon and widefield imaging experiments in awake, head-fixed mice with virally expressed CaMKII-GCaMP6f (neurons) and acutely injected with Texas Red dye (vasculature). Two-photon imaging enables calcium transients of several neurons and blood flow speeds in adjacent capillaries to be simultaneously recorded. Widefield imaging gives pixel-by-pixel correlations between tissue calcium transients and changes in blood flow speed (imaged via laser speckle contrast analysis) and blood volume/oxygenation (imaged via intrinsic optical imaging). Preliminary results indicate a prolonged elevation of blood flow speed and overall blood flow response to drifting grating visual stimulation after psilocybin administration. Averaged over the duration of visual stimulation, vessels in non-psilocybin conditions (Pre Control, Post Control, Pre Psilocybin) show a ~9% increase in blood flow speed, while vessels in psilocybin conditions (Post Psilocybin) show a ~16% increase in blood flow speed. Altered NVC due to the action of psychedelics on the vasculature could indicate important considerations for the interpretation of human neuroimaging of psychedelic action.

Disclosures: **R.T. Zirkel:** None. **C. Liao:** None. **M. Isaacson:** None. **D.A. Rivera:** None. **M. Yi:** None. **A.C. Kwan:** None. **N. Nishimura:** None. **C.B. Schaffer:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.15/M32

Topic: G.09. Drugs of Abuse and Addiction

Title: Characterizing non-psychedelic psychedelics: phenotypic fingerprinting of lisuride and LSD

Authors: *J. L. KING[1], D. EFFINGER[2], J. R. CALDERON[2], J. R. STRONG[2,3], C. BASQUEZ-PFEIFER[4], S. M. THOMPSON[2];
[2]Psychiatry, [1]Univ. of Colorado Anschutz Med. Campus, Aurora, CO; [3]Psychiatry, Univ. of Colorado Anchutz Med. Campus, Aurora, CO; [4]Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: Psychedelics provide rapid and persistent symptom improvements for a range of neuropsychiatric disorders, including depression. However, their implementation as a widespread clinical intervention may be hindered by the characteristic alterations in perception and consciousness they produce (i.e. the hallucination). Psychedelics are potent agonists at many serotonin receptors (5HTRs). Specifically, $5HT_{2A}$Rs mediate psychedelic-induced perceptual alterations and may also be essential to the therapeutic response. To harness the clinical benefits of psychedelics while lowering economic barriers, biased $5HT_{2A}$R agonists that do not elicit visual hallucinations are currently being commercially developed. The head twitch response (HTR) is a widely used preclinical assessment of psychedelic responses. However, it is unknown whether the absence of a HTR is sufficient to identify truly non-hallucinogenic compounds. Here we report results comparing the effects of lysergic acid diethylamide (LSD) and lisuride, a potent $5HT_{2A}$R agonist that does not cause HTRs, in a variety of assays in mice. Lisuride (0.5mg/kg), but not LSD (0.1mg/kg), produced a profound impairment of motor behavior in the open field and on the rotarod. Lisuride also impaired performance in an ethologically relevant cognitive task, the puzzle box. Both motor and cognitive effects of lisuride persisted when $5HT_{2A}$Rs were pharmacologically blocked with MDL100,907 (0.5mg/kg). Lisuride and LSD both produced unique alterations in electroencephalograms recorded over the prefrontal cortex. Combined, these results suggest that although lisuride may not be acting as a traditional psychedelic, it does impact both motor and cognitive function. Further, robust preclinical phenotypic characterization beyond the HTR is important for identifying non-hallucinogenic compounds to move forward for clinical development.

Disclosures: J.L. King: None. **D. Effinger:** None. **J.R. Calderon:** None. **J.R. Strong:** None. **C. Basquez-Pfeifer:** None. **S.M. Thompson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ProNova. F. Consulting Fees (e.g., advisory boards); Otsuka Pharmaceutical, Terran Biosciences, Althea PBC.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.16/M33

Topic: G.09. Drugs of Abuse and Addiction

Support: Templeton World Charity Foundation
Tiny Blue Dot Foundation

Title: Do mice trip? Investigations into the behavioral and neural modulations of the classic psychedelic drug psilocybin

Authors: *D. G. WYRICK[1], L. MARKS[2], Y. NAHAS[3], L. D. CLAAR[1], P. SEYFOURIAN[4], C. KOCH[5], I. REMBADO[1], M. A. BUICE[5];
[1]Allen Inst., SEATTLE, WA; [2]Sch. of Biochem. and Immunol., Tomas Ryan Lab. / TBSI, Dublin, Ireland; [3]Brain and Consciousness, Allen Inst., Seattle, WA; [4]UBC, Burnaby, BC, Canada; [5]Allen Inst. For Brain Sci., Seattle, WA

Abstract: We are studying the classic psychedelic drug psilocybin in a unique experimental setup which allows us to simultaneously record thousands of neurons and the local field potential via Neuropixels electrodes, together with electroencephalography in head-fixed mice on a running wheel. This setup provides us with an opportunity to quantify the behavioral and neural modulations due to psilocybin (delivered i.p.) across multiple levels of granularity, including changes in firing rate and pairwise functional connectivity (FC) at the level of single neurons. Human neuroimaging studies have reported a reorganization of FC within and between resting state networks due to psychedelics, enhancing communication between networks while diminishing the connectivity within individual networks, including the default mode and salience networks. While these changes in FC are well documented in humans using indirect measures of neural activity, how this manifests at the level of spiking neural populations within and between cortical and thalamic areas has not been investigated yet. Accurately assessing the FC of a network is a fundamental goal in computational neuroscience, as it is informative of the dynamical relationships between neurons and brain areas interacting in a network. Here we estimate a directed measure of FC, based on a delay-embedding, time-series forecasting approach to quantify the interactions between neurons distributed across the mouse cortex and thalamus under the psychedelic state. We show that the behavioral and neural modulations due to psilocybin are inextricably linked. The overall magnitude of FC - both delay embedding and correlation-based measures - decreases with the running speed of the animal, highlighting the necessity for quantifying and conditioning on behavior. Preliminary results suggest a complex relationship between how psilocybin and behavior alter the structure of functional connections in the brain at the level of spiking neurons. Conditioning on similar behavioral states pre and post psilocybin, we show that our measure of directed FC reveals a complex network reorganization due to psilocybin, with certain thalamo-cortical connections strengthening and other cortico-cortical connections decreasing. Our current focus of inquiry is how these changes in connectivity map onto models of psychedelic action, thereby providing insights into potential mechanisms.

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Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.17/M34

Topic: G.09. Drugs of Abuse and Addiction

Support: Ekam Imaging Inc.

Title: Dose-dependent changes in global brain activity and functional connectivity following exposure to psilocybin: a BOLD MRI study in awake rats.

Authors: *N. CAVALLARO[1], P. KULKARNI[2], R. ORTIZ[3], H. B. BRADSHAW[4], C. FERRIS[5];
[1]Northeastern Univ., East Freetown, MA; [2]Ctr. for Comparative NeuroImaging, Worcester Polytechnic Inst., Worcester, MA; [3]Pharmaceut. Sci., Northeastern Univ., Boston, MA; [4]Psychological and Brain Sci., Indiana Univ. Bloomington, Saco, ME; [5]Northeastern Univ. CTNI, Boston, MA

Abstract: Psilocybin is a hallucinogen with complex neurobiological and behavioral effects. This is the first study to use MRI to follow functional changes in brain activity in response to different doses of psilocybin in fully awake, drug naive rats. We hypothesized that LSD would show a dose-dependent increase in activity in the prefrontal ctx and thalamus, while decreasing hippocampal activity. Female and male rats were given IP injections of vehicle or psilocybin in doses of 0.03, 0.3, and 3.0 mg/kg while fully awake during the imaging session. Changes in BOLD signal were recorded over a 30 min window. Approximately 35 min post injection data for resting state functional connectivity were collected All data were registered to rat 3D MRI atlas with 173 brain regions providing site-specific changes in global brain activity and changes in functional connectivity. Treatment with psilocybin resulted in a significant dose-dependent increase in positive BOLD signal. The areas most affected by the acute presentation of psilocybin were the somatosensory cortex, prefrontal cortex, basal ganglia and thalamus. There was a significant dose-dependent global increase in functional connectivity, highlighted by hyperconnectivity to the cerebellum. Brain areas hypothesized to be involved in loss of sensory filtering and organization of sensory motor stimuli such as the claustrum and the cortico-basal ganglia-thalamic-cortical loop were all affected by psilocybin in a dose-dependent manner. Indeed, the general neuroanatomical circuitry associated with the psychedelic experience was affected but the direction of the BOLD signal and pattern of activity between neural networks was inconsistent with the human literature.

Disclosures: **N. Cavallaro:** None. **P. Kulkarni:** None. **R. Ortiz:** None. **H.B. Bradshaw:** None. **C. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CFF and PK have a partnership interest in Ekam Imaging Inc. a company that develops RF electronics and 3D MRI atlases for animal research..

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.18/M35

Topic: G.09. Drugs of Abuse and Addiction

Title: Psilocybin as a treatment for microstructural and functional alterations following repetitive mild head injury: A preclinical MRI study

Authors: *E. K. BRENGEL[1], B. M. AXE[1], A. MAHESWARI[1], C. SAWADA[1], S. BALAJI[1], R. UTAMA[1], T. J. WOODWARD[2], H. B. BRADSHAW[2], M. A. GITCHO[3], P. P. KULKARNI[1], C. F. FERRIS[1];
[1]Ctr. for Translational Neuroimaging, Northeastern Univ., Boston, MA; [2]Psychological and Brain Sci., Indiana Univ., Bloomington, IN; [3]Biol. Sci., Delaware State Univ., Dover, DE

Abstract: Psilocybin, a psychedelic 5HT-2A agonist, has garnered attention as an effector of neuroplasticity. While its therapeutic effects have been hypothesized to extend to traumatic brain injury, it has not yet been tested. In this study, short-term and lasting effects of psilocybin treatment on brain health following repetitive mild traumatic brain injury (rmTBI) were examined using an array of preclinical neuroimaging, behavioral, and histological assays. Adult female Wistar rats (N=24) were housed on a reverse light-dark cycle and subjected to awake closed-head momentum exchange mTBI or sham injury once daily for three days, followed by psilocybin or vehicle injection. On Day 3, plasma samples were collected for psilocin and lipid mTBI biomarker quantification before rats received diffusion weighted imaging (DWI) on a 7T MRI scanner for microstructural examination. Cognitive behaviors were assessed with Head Twitch, Open Field, and Novel Object Recognition tests. Motor skills were assessed with Rotarod and Tapered Balance Beam tests. Three weeks later, microstructural recovery was assessed with DWI, neurovascular coupling was measured by fMRI with CO_2 challenge, and circuitry was measured with awake functional connectivity scanning (FC). Brains were collected for analysis of inflammatory protein expression. Day 3 DWI indicates apparent diffusion coefficient (ADC) is increased globally by rmTBI and partially restored by psilocybin treatment ($p<0.00005$). This pattern was reflected in the prefrontal cortex, sensory cortex, and hippocampus ($p<0.05$), while psilocybin treatment completely prevented rmTBI-induced ADC increases in the thalamus, basal ganglia, and olfactory system ($p<0.005$). The opposite was found in the midbrain dopaminergic system, where ADC reduction was observed and restored by psilocybin treatment ($p<0.05$). By Day 22, all ADC changes were resolved; however, lasting functional alterations were observed. fMRI indicates a hyperactive BOLD response to 5% CO2 challenge is induced by prior rmTBI. This functional alteration is limited globally by psilocybin treatment and prevented entirely in the prefrontal cortex and olfactory system ($p<0.0005$). Behavioral effects were minimal. Analysis of FC, twitch, plasma, and protein remains underway. These findings contribute to a growing body of evidence supporting the therapeutic potential of psilocybin treatment for rmTBI. Further analysis is needed to elucidate the mechanisms and consequences of the observed changes in tissue diffusivity and neurovascular coupling, and future research must investigate the use of psilocybin to prevent long-term rmTBI-associated neurodegeneration.

Disclosures: E.K. Brengel: None. **B.M. Axe:** None. **A. maheswari:** None. **C. Sawada:** None. **S. Balaji:** None. **R. Utama:** None. **T.J. Woodward:** None. **H.B. Bradshaw:** None. **M.A.**

Gitcho: None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ekam Imaging. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ekam Imaging.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.19/M36

Topic: G.09. Drugs of Abuse and Addiction

Support: T32GM148403
R01MH084894

Title: Stereoselective Effects of MDMA on Mouse Frontal Cortex Structural Plasticity via 5-$HT_{2A}R$

Authors: *M. C. GAINES-SMITH[1], J. GONZÁLEZ-MAESO[1], J. YOUNKIN[1], M. DUKAT[2], J. MALTMAN[3];
[1]Physiol. and Biophysics, [2]Medicinal Chem., Virginia Commonwealth Univ., Richmond, VA; [3]Virginia Commonwealth Univ., Richmond, VA.

Abstract: Psychoactive serotonergic drugs are gaining popularity as potential therapeutics for mental health pathologies, showing promising potential in treating individuals with diagnoses ranging from major depressive disorder (MDD) to treatment resistant post traumatic stress disorder (PTSD) after as little as one dose. Upon completing phase 3 human trials, entactogen 3,4-methylenedioxymethamphetamine (MDMA) showed a reduction in both PTSD and MDD symptoms in participants, however the complete mechanism of its success is still not understood. This project aims to further elucidate the therapeutic mechanism of MDMA, providing both in vivo and in vitro data supporting the drug's proposed mechanism of action. This research proposes that the therapeutic action of MDMA is mediated by its interaction at the serotonin 2A receptor (5-$HT_{2A}R$). The 5-$HT_{2A}R$ is of interest as it is implicated as the receptor responsible for psychedelic activity when agonized, and in the potentially therapeutic effects seen in psychoactive serotonergic drugs. In vitro, HEK293 cells stably transfected with the 5-$HT_{2A}R$ were utilized to conduct competitive radioligand binding of MDMA isomers against [^{3}H]ketanserin at the 5-$HT_{2A}R$. Additionally, intracellular Ca^{2+} quantification was conducted to determine agonism of 5-$HT_{2A}R$. In vivo, 5-$HT_{2A}R$ agonism was measured via head twitch response (HTR) in C57BL/6 mice. Additionally, prefrontal cortex dendritic spine morphology is being compared in mice administered R or S MDMA isomers. Despite having a lower binding affinity for the 5-$HT_{2A}R$, the S-isomer of MDMA induced the highest intracellular calcium release in HEK293 cells stably transfected with 5-$HT_{2A}R$, indicating partial agonism at the receptor. Similarly, the S isomer showed partial agonist activity as measured by HTR. It is anticipated that dendritic spine data will be stratified according to this trend.This suggests that

MDMA has significant action at the 5-HT_{2A}R that could potentially be classified as therapeutically relevant.

Disclosures: **M.C. Gaines-Smith:** None. **J. González-Maeso:** A. Employment/Salary (full or part-time):; Virginia Commonwealth University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Terran Biosciences. **J. Younkin:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.20/M37

Topic: G.09. Drugs of Abuse and Addiction

Support: EKAM Imaging Inc.

Title: Adolescent exposure to psilocybin alters the perception of rewarding and fearful stimuli in adulthood. An awaking MRI studying in male and female mice.

Authors: *S. MASADI;
Ctr. for translational Neuroimaging, Northeastern Univ., boston, MA

Abstract: Psilocybin is being used to treat psychiatric disorders. Single or multiple small doses can have rapid and long lasting effects that persist for month. These effects are due in part to psilocybin's effect on neuroplasticity, e.g. increase synaptic connectivity helping to reduce aversive motivation in response to fearful stimuli. Indeed, in a clinical setting healthy volunteers show a reduction in emotional reactivity to fearful faces. There is a growing literature that hallucinogens and behavioral phenotypes in general can affect one's perception of their environment. In a previous study we tested this notion in fragile X rats a model of autism spectrum disorder, asking if these rodents differed in their sensitivity to fearful and rewarding stimuli. Using functional magnetic resonance imaging we presented awake FX rats with the smell of almond a rewarding odor or the smell of a predator, an aversive odor during the imaging session. To our surprise the FX rats showed normal brain activity to fear but dysfunctional activity to reward. We repeated that study in healthy mice treated in adolescence with an oral gave of 3.0mg/kg dose of psilocybin given every other day over 10 days for a total of five treatments. Three months later mice were imaged for changes in brain activity and connectivity while fully awake in response to almond odor and fox scent. Imaging data was registered to a 3D MRI mouse atlas with 140 brain regions provided site-specific changes in BOLD signal. The change in global brain activity and connectivity associated with the basal ganglia, thalamus, sensory motor cortex and cerebellum was significantly different for both stimuli in mice with a history of psilocybin exposure as compared to vehicle controls. There was no significant sex difference.

Disclosures: S. Masadi: None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.21/M38

Topic: G.09. Drugs of Abuse and Addiction

Title: Changes in brain structure and function following exposure to oral psilocybin during adolescence in female and male mice: A multimodal MRI study

Authors: *I. SAHOO[1], A. CHANG[1], P. P. KULKARNI[1], C. F. FERRIS[1], S. MASADI[2]; [1]Ctr. for Translational Neuroimaging, Northeastern Univ., Boston, MA; [2]Northeastern Univ., boston, MA.

Abstract: Amidst the War on Drugs in 1971, the United Nations classified LSD and other psychedelic drugs as Schedule 1 substances. However, in the past decade, there has been a resurgence of scientific interest in psilocybin. Small clinical trials report promising results in treating MDD, end-of-life distress, PTSD, and alcoholism. How does psilocybin alter brain neural circuitry to affect behavior? Does exposure to psilocybin in adolescence have long-lasting effects on brain structure and function? To address these questions we studied male and female mice exposed to LSD during adolescence for changes in neurobiology in adulthood using multimodal MRI and behavior assays testing for motor control, cognitive function, and emotion. Male and female mice (18-22 g weight) were exposed to vehicle (n=12), a single oral dose of psilocybin (n=12) every other day for 10 days or a total of five doses. All mice were given an oral gavage of 100 µl having an approximate amount of 3.0 mg/kg psilocybin. All treatments started on postnatal day 51. All experiments were conducted under dim red illumination between 10:00 hrs and 18:00 hrs to avoid the transitions between the L-D dark cycles. Mice were imaged and tested for behavior as young adults (90 to 150 days of age). Male and female mice exposed to psilocybin multiple times presented with changes in gray matter microarchitecture over much of the brain as compared to vehicle. Resting state functional connectivity was altered in thalamocortical circuitry.

Disclosures: I. Sahoo: None. **A. Chang:** None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EKAM Imaging. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EKAM Imaging.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR041.22/M39

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH R01 NS045193
NIH R01 MH115750
NIH U19 NS104648

Title: Accelerated acquisition of a sensory evidence accumulation after single-dose psilocybin

Authors: *M. KISLIN, E. SEFIK, C. JUNG, S. S. WANG;
Princeton Univ., Princeton, NJ

Abstract: To probe psilocybin effects on aspects of cognition in a parametrically well-defined task, we used an established paradigm for learning in mice that includes a complex shaping procedure of a perceptual decision-making task, that requires accumulation of sensory evidence in working memory (Deverett et al. 2018, 2019; Pinto et al. 2018).
In this evidence accumulation task, mice receive air puffs to left and right whiskers over a period of several seconds. Then, after a pause, they are rewarded with a drop of water on correctly selecting a spout on the side with more air puffs. This task is rich in quantitative detail and lends itself to detailed analysis and quantitative modeling.
We probed the long-term effects of a single dose of psilocybin over a period of task acquisition 2-52 days after treatment. Psilocybin-experienced mice (2 mg/kg delivered via intraperitoneal injection) acquired the task at high rates, matching the upper quartile of vehicle-treated mice. Effects were large (0.7 to 1.4 standard deviation) for selected steps of task acquisition requiring a change in the animal's control over its choice. These accelerated steps included prompting the animal to make licks on the correct side (level 1) and progressive lengthening from 200 ms to 800 ms of the delay between the end of evidence to the prompt to lick (levels 4 and 5). However, learning steps involving changes in the duration of sensory evidence (levels 2 and 3) and the integration of evidence (levels 6 and 7) were not accelerated. In this way improvements in task acquisition arising from psilocybin are restricted to control over action, but not working memory capacity.
We are now examining the dependence of psilocybin-accelerated learning on serotonergic, neurotrophic, and stress pathways. We are also using advanced modeling techniques, including a generalized linear model-hidden Markov model (GLM-HMM) (Oostland, Kislin et al. 2021, bioRxiv) to identify occupancy of behavioral states during learning and a drift-diffusion model to quantify alterations in the parameters of evidence accumulation during performance of the learned task.
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- Oostland M, Kislin M et al. 2021,bioRxiv 2021.12.23.474034

Disclosures: M. Kislin: None. **E. Sefik:** None. **C. Jung:** None. **S.S. Wang:** None.

Poster

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH R01 NS045193
NIH R01 MH115750
NIH U19 NS104648
CV Starr Fellowship (Starr Foundation)

Title: Dependence of psilocybin-induced dendritic spine dynamics on serotonergic and neurotrophic mechanisms

Authors: *E. SEFIK[1], M. KISLIN[1], C. O'SHEA[1,2], L. A. LYNCH[1], S. R. JANARTHANAN[1], S. S. WANG[1];
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Rutgers Robert Wood Johnson Medical School, Piscataway, NJ

Abstract: Dendritic spines, micron-sized actin-rich structures that act as sites of synaptic input, undergo dynamic structural changes and support behavioral plasticity. In the mammalian neocortex, spine density, turnover, and motility peak during early postnatal development and diminish with age. Psychedelic compounds like psilocybin have recently been found in adult mice to alter dendritic spine structure, with rapid and persistent increases seen in spine formation. These findings suggest that psilocybin has the potential to induce functional change in the mature brain and potentially reopen windows of plasticity. However, human data on psilocybin's effects on cognition are mixed, and direct correlations between psilocybin's effects on spine structure and cognitive function are lacking. Furthermore, the receptor mechanisms mediating psilocybin's actions are yet to be fully elucidated. Emerging findings from our laboratory reveal that psilocybin accelerates the acquisition of motivated behavior components in a sensory evidence accumulation task. In the present project, we test the hypothesis that psilocybin-induced cognitive improvements in mice are associated with changes in cortical spine density and morphology. We are employing high-resolution confocal microscopy and DiOlistic labeling, combined with a deep learning-based framework (DeepD3) for automated spine identification, to quantify spine density and size in basal and apical dendrites of cortical pyramidal neurons across three distinct brain regions in mice following intraperitoneal administration of a single dose of psilocybin (2 mg/kg). We are testing mice with psilocybin, with evidence accumulation training, and with both psilocybin and evidence accumulation (3 conditions; n = 8 mice per group, 180 dendrites per mouse). Effects at both early and final stages of behavioral shaping are being investigated. Finally, we are exploring the dependence of psilocybin's actions on serotonergic and BDNF/TrkB receptor mechanisms through pharmacological experiments. The findings may yield novel insights into the mechanisms underlying psilocybin's therapeutic potential, aligning with its significance highlighted by its designation by the FDA as a "breakthrough therapy."

Disclosures: **E. Sefik:** None. **M. Kislin:** None. **C. O'shea:** None. **L.A. Lynch:** None. **S.R. Janarthanan:** None. **S.S. Wang:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.24/N1

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R35NS097287

Title: Mesoscale cortical 2-photon (2p) imaging in mice shows enhanced default-mode network activation during periods of psychedelic (DOI)-induced infra-slow pupil oscillations

Authors: *E. D. VICKERS[1], M. B. JOHNSON[1], L. MAZZUCATO[2], D. A. MCCORMICK[2]; [1]Inst. of Neurosci., Univ. of Oregon, Eugene, OR; [2]Dept. of Biol., Univ. of Oregon, Eugene, OR

Abstract: Neuroscience is undergoing a resurgence in the study of psychedelic drugs, in part because they have been shown to aid in alleviation of depression and drug addiction in humans, and to reopen critical periods of brain plasticity in rodents[1]. However, it is unknown how psychedelics act in the brain to drive the beneficial long-term brain plasticity underlying these therapeutic effects. We sought to fill a gap in the field of psychedelics neuroscience research by performing large-scale 2p imaging of up to ~10,000 excitatory neurons at a time across all of mouse dorsolateral cortex[2] during spontaneous behavior in the presence of the psychedelic 2,5-Dimethoxy-4-iodoamphetamine (DOI; 10 mg / kg, SC).

We adopted a “before vs. after” spontaneous behavior design with 90 min 2p recording sessions, with sham injections on day 0 and DOI on day 1 (n=10, N=6; 3 male, 3 female; CaMKII-Cre x Ai148 or Ai162). We regularly observed forepaw stereotypies at the beginning of the post-DOI session. Following an initial period of DOI-induced neurobehavioral “disorganization” (54.5 ± 32.2 min), mice (n=8/10, N=5/6) unexpectedly entered into an extended period characterized by a high amplitude (54.7 ± 18.2% depth modulation), regular (0.004 ± 0.002 Hz), infra-slow pupil oscillation (0.03 ± 0.01 Hz, duration = 26.0 ± 22.7 min), during which the mouse remained awake. Neural activity during this period was wave-like and involved areas implicated in the rodent default mode network (DMN[3,4]), with a widespread cortical population activated at the apex of the oscillation (i.e. at max pupil diameter, coinciding with small wheel-balancing movements and whisker twitching), and a concentrated population of neurons over lateral cortex (i.e. primary, dorsal, and ventral auditory, and somatosensory mouth, nose, and supplemental somatosensory cortices) activated at the trough of each oscillation.

We show here that cortical dynamics under DOI, which may continue to evolve after the drug reaches a steady state concentration in the brain, are driven by an initial disorganization of behavior for ~30-50 min, followed by a decoupling of detailed neural activity from behavior at faster timescales, along with enhanced infraslow oscillatory wave-like activity of the DMN over the next 1-2 hrs. We hypothesize that repeated pairing of novel neural activity patterns with a

wave-like oscillation may drive induction of synaptic plasticity leading to long-term changes in brain activity and behavior underlying phenomena observed in humans and rodents related to depression, addictions, and critical-period plasticity.
Refs: [1]Nardou at al, 2023. [2]Vickers & McCormick, 2024 (eLife). [3]Raichle et al, 2001. [4]Raichle, 2015.

Disclosures: E.D. Vickers: None. **M.B. Johnson:** None. **L. Mazzucato:** None. **D.A. McCormick:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.25/N2

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant F31DA055445 (NIDA)
T32 DA035200 (NIDA)

Title: Psychedelics Regulate Cocaine-induced Behavioral and Neuronal plasticity in the Claustrum

Authors: *T. ANDERSON[1], N. TAVAKOLI[1], P. I. ORTINSKI[2];
[2]Neurosci., [1]Univ. of Kentucky, Lexington, KY

Abstract: Psychedelic drugs have recently attracted widespread research and public interest. Early clinical outcomes probing the potential of psychedelics for the treatment of substance use are promising, but a large gap remains in understanding of mechanisms by which psychedelics may achieve therapeutic outcomes. It has recently been proposed that psychedelics improve cognitive flexibility to enhance adaptive behavioral strategies. Cognitive flexibility deficits are characteristic of substance use disorders, contributing to difficulties with abstinence and making relapse more likely to occur. We explored the hypothesis that psychedelic drugs may engage neurons in the claustrum (CLA), a subcortical nucleus with extensive cortical projections and a high density of serotonin receptors, to induce neuronal plasticity linked to cocaine-seeking behaviors.
Using qPCR and RNAscope, we demonstrate that 5-HT2A and 5-HT2C receptors subtypes on both glutamatergic and GABAergic neurons account for the bulk of serotonin receptor expression in the CLA, but that other subtypes (notably 5-HT1A) are also expressed at substantial levels. Whole-cell patch-clamp electrophysiology indicated that 5-HT inhibits intrinsic excitability and glutamatergic neurotransmission in CLA neurons projecting to the anterior cingulate cortex (CLA-ACC neurons). In contrast, we found that DOI, a potent psychedelic 5-HT2 receptor agonist, excites CLA-ACC glutamatergic signaling via the 5-HT2C, but not the 5-HT2A, receptors. At the behavioral level, we demonstrate that contingent cocaine self-administration, but not the non-contingent (i.p.) injections of cocaine, produced cognitive

flexibility deficits in the set-shift task. Preliminary data indicate that microinjections of DOI into the CLA impact both cognitive flexibility performance and electrophysiological signatures of CLA-ACC neuron excitability during cocaine withdrawal. For example, we find reduced sensitivity of CLA-ACC neurons to membrane effects of a 5-HT1A antagonist in cocaine-experienced animals relative to yoked saline controls. Finally, we show that DOI administration unlocks spike-timing dependent long-term potentiation in CLA-ACC neurons that is absent under control conditions.

Disclosures: T. Anderson: None. **N. Tavakoli:** None. **P.I. Ortinski:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.26/N3

Topic: H.02. Perception and Imagery

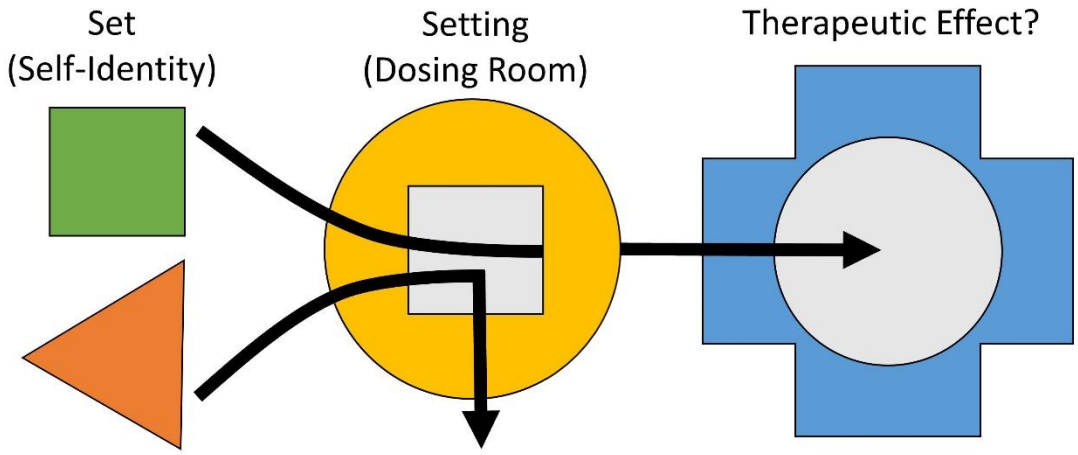
Support: WARF URI 2021
NTP Training Grant 5T32NS105602
NIH NCATS TL1TR002375 & UL1TR002373

Title: Poiesis (psychedelic outcomes: interaction of environment and self-identity) - importance of naturalistic elements and religion/spirituality in a psychedelic dosing space

Authors: *S. LEE[1,2], C. J. WENTHUR[3];
[1]UW-Madison, Madison, WI; [2]University of Wisconsin - Madison Neuroscience Training Program, Madison, WI; [3]Pharm., Univ. of Wisconsin - Madison. Psychoactive Pharmaceut. Investigation Program, Madison, WI

Abstract: Psychedelic-assisted psychotherapy has shown promising therapeutic effects for mental illnesses. However, marginalized racial and ethnic groups remain underrepresented in psychedelic studies. Greater inclusion of minorities may indirectly influence therapeutic outcomes, acting as a therapeutic filter in the psychedelic dosing room. We hypothesize that the psychedelic dosing room environment influences one's experiences based on connectivity to one's racial-ethnic self-identity. Online surveys (n=141; 49% BIPOC), filled out by members of psychedelic societies, included five response sections on visual analogue scale: perceived self-identity (age, gender, race/ethnicity, religion/spirituality) connectivity and overall reaction to the dosing room and 15 art objects within the space. A community interest group reacted to an art library and provided their preference. Results were analyzed using multiple linear regression and dominance. The members from psychedelic societies viewed 14/15 art objects and the dosing room positively. However, there are no significant differences between Non-Hispanic White and others who do not identify with this race-ethnicity in overall reaction across all art objects and dosing room. Our linear model with self-identity as factors significantly modelled the overall reaction in 12/15 art objects ($r2 = .15$ to $.75$; $p = .03$ to $p < .0001$) but not the dosing room.

Dominance analysis revealed that religion/spirituality had complete dominance over all other dimensions of self-identity in 14/15 art objects and the dosing room. The community interest group preferred natural-like artwork from the art library, especially those with plants ($p = 0.01$) and landscape ($p = 0.02$) elements. We find that religion/spirituality had the greatest impact on perceived connectivity to art objects being in the dosing room. With increasing movement towards psychedelic-assisted psychotherapy, we recommend crafting the psychedelic dosing space with the themes we identified here and acknowledging participants' lived experiences.



Disclosures: S. Lee: None. **C.J. Wenthur:** 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.; CJW has received funding / support from Usona Institute, Psilera Inc., and Mike and Mary Shannon for the study of psychedelics.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); received funding/support from Usona Institute for the study of psychedelics.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.27/N4

Topic: G.08. Other Psychiatric Disorders

Title: Dual 5-HT_{1A} and 5-HT_{2A} Receptor Ligand SUVN-2206043 shows Antipsychotic and Antidepressant Like Effects in Animal Models

Authors: *P. JAYARAJAN, R. ABRAHAM, R. KALLEPALLI, P. ALABADE, S. MANCHINEELLA, T. NARASIMHULA, A. SHAIKH, V. PALACHARLA, V. BENADE, R. SHYAM, S. PANDEY, Y. YASHASWI, S. PETLU, R. SUBRAMANIAN, R. NIROGI; Suven Life Sci. Ltd., Hyderabad, India

Abstract: Psychiatric disorders impact individuals irrespective of age groups, socioeconomic backgrounds, and geographical regions resulting in personal suffering, impaired daily functioning, and extensive societal costs. Patients with psychiatric disorders also suffer from comorbid medical conditions and are at higher risk of premature death. Most of the currently prescribed drugs to treat psychiatric disorders are arguably no more effective than the first generation of psychiatric agents. In addition, existing therapies are associated with side effects such as motor disturbances, metabolic disorders and unwanted cardiac effects. Newer, more effective, and better-tolerated agents are desperately needed. SUVN-2206043 is a new chemical entity that targets primarily 5-HT_{1A} and 5-HT_{2A} receptors. SUVN-2206043 acts as a partial agonist at 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors. Pharmacokinetics studies in Wistar rats indicated that SUVN-2206043 has excellent bioavailability (50%) and high brain penetration (C_b/C_p ratio of ~2). At doses ranging from 0.3 to 30 mg/kg, SUVN-2206043 significantly antagonized both MK-801 and amphetamine-induced hyperlocomotion. SUVN-2206043 was found to have good receptor occupancy for 5-HT_{2A} and 5-HT_{1A} receptors at doses found to be efficacious in rats. It also showed antidepressant-like effects in the mouse forced swim test, tail suspension test, and chronic mild stress models at doses ranging from 0.3 to 3 mg/kg. SUVN-2206043 was devoid of motor side effects at doses up to 30 mg/kg in the catalepsy and rotarod assay. Preliminary toxicity studies did not signal any concerns for further development. SUVN-2206043 could be a promising newer, more effective, and better-tolerated agent for the treatment of psychiatric disorders like schizophrenia and depression.

Disclosures: P. Jayarajan: A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Kallepalli:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **P. Alabade:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **S. Manchineella:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **T. Narasimhula:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **A. Shaikh:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **V. Palacharla:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Shyam:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **Y. Yashaswi:** None. **S. Petlu:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.28/N5

Topic: G.08. Other Psychiatric Disorders

Title: Novel 5-HT_{2A}selective agonists with well-characterized PK profile and short duration of action

Authors: *A. VASILKEVICH[1], A. L. HALBERSTADT[2], J. DUAN[1], C. R. MERRITT[3], K. A. CUNNINGHAM[3], J. MCCORVY[4], A. KOZIKOWSKI[5], J. PEDERSEN[1];
[1]Bright Minds Biosci., New York, NY; [2]UCSD, La Jolla, CA; [3]Ctr. for Addiction Res., Univ. of Texas Med. Br., Galveston, TX; [4]Cell Biology, Neurobio. & Anat., Med. Col. of Wisconsin, Milwaukee, WI; [5]Georgetown Univ. Med. Ctr., Georgetown, WA

Abstract: Psychedelic compounds have emerged as rapid-acting novel and effective treatments for a range of psychiatric disorders such as depression, PTSD, addictions, and other CNS disorders. However, their psychedelic or psychoactive effects, polypharmacology, and off-target activity create serious safety liabilities, in particular, off-target activity at the hERG channel and the 5-HT_{2B} receptor that result in cardiac risks. Finally, very long and unpredictable in-vivo human PK/PD properties make first-generation psychedelics less than optimal as modern rapid-acting antidepressants. Bright Minds Biosciences, has developed the first-in-class highly selective 5-HT_{2A} receptor agonist, BMB-202, designed to have a short duration of action. BMB-202 was investigated at 5-$HT_{2A/2B/2C}$ receptors using Gq dissociation as measured by Bioluminescence Resonance Energy Transfer (BRET) *in vitro*. In this assay, BMB-202 had higher potency at the 5-HT_{2A} receptor (EC_{50} = 5.9 nM with E_{max} = 97% of 5-HT response) than psilocin (EC_{50} = 8.3 nM with Emax = 82% of 5-HT response) and lower potency at 5-HT_{2B} and 5-HT_{2C} receptors. *In vivo*, BMB-202 was assessed in the head-twitch response assays in C57BL/6J mice and induced the behavior with ED_{50} = 2.69 mg/kg. In the olfactory bulbectomized (OBX) Sprague-Dawley rat model, BMB-202 reduced long-lasting hyperactivity in a novel/stressful environment and had enduring effects similar to psilocybin. BMB-202 is fully profiled in ADME/PK and did not produce significant adverse effects *in vivo*. Preclinical data supports the notion that BMB-202 may have long-term antidepressant effects in humans after single-dose administration, with an estimated duration of action of ~2 hours. This research work was funded by Bright Minds Biosciences.

Disclosures: A. Vasilkevich: A. Employment/Salary (full or part-time):; Bright Minds Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bright Minds Biosciences. **A.L. Halberstadt:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Bright Minds Biosciences. **J. Duan:** F. Consulting Fees (e.g., advisory boards); Bright Minds Biosciences. **C.R. Merritt:** 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.; Bright Minds Biosciences. **K.A. Cunningham:** 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.; Bright Minds Biosciences. **J. McCorvy:** 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.; Bright Minds Biosciences. **A. Kozikowski:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

property rights/patent holder, excluding diversified mutual funds); Bright Minds Biosciences. **J. Pedersen:** A. Employment/Salary (full or part-time):; Bright Minds Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bright Minds Biosciences.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.29/N6

Topic: G.08. Other Psychiatric Disorders

Support: NIH: grant number 2R25NS080686
NIH: grant number R21MH105846
NIH: grant number R01NS066019
NIH: grant number R01NS047557
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NSF: 1460880
NSF: 1950649
Fulbright Scholarship: no number
NYU Dean's Undergraduate Research Fund: no number
NYU Research Challenge Fund: no number
Vulnerable Brain Project Grant: no number
The Klarman Foundation Grant Program in Eating Disorders Research: no number
Baszucki Group Grant
NSF-REU Grant DBI-1950649

Title: Deducing Mechanisms of Sub-Anesthetic Ketamine-Induced Relief from Anorexia-Like Symptoms in Adolescent Female Mice through Examining the Role of AMPA Receptors in the Prefrontal Cortex

Authors: *B. XU, Y.-W. CHEN, C. CARRASCO, R. TEMIZER, C. J. AOKI;
New York Univ. Ctr. for Neural Sci., New York, NY

Abstract: Anorexia nervosa is a deadly eating disorder characterized by severe voluntary food restriction and compulsive exercising, resulting in extreme body weight loss. Sub-anesthetic dose of ketamine holds promise as a treatment. In a previous behavioral study, 16 adolescent female C57BI/6 J mice underwent the activity-based anorexia (ABA) model, which included acclimation to an exercise wheel and 2 cycles of food restriction (ABA1, ABA2), each followed by a recovery period. A single intraperitoneal dose of 3mg/kg or 30mg/kg ketamine was given in ABA1. The 30mg/kg dose ameliorated anorexia-like symptoms significantly by increasing food consumption, body weight, and reducing excessive wheel running. The effective 30mg/kg dose also increased resilience by reducing severity of relapse, quantified as reduction of wheel

running during ABA2 relative to ABA1 (ABA2-ABA1). The 3mg/kg dose was less consistent in its efficacy (Chen et al., 2018, DOI: 10.1002/eat.22937). This project examined the contribution of prefrontal cortical (PFC) AMPA receptors (AMPAR) in the differential efficacy of the two doses. The levels and locations of AMPAR at excitatory synapses onto dendritic spines (axo-spinous) of pyramidal neurons (PN) and dendritic shafts (axo-shaft) of GABA interneurons (GABA-IN) were quantified using immunocytochemistry and electron microscopy, and correlation analysis with the behavior traits was performed. Thus far, 9 of the 16 animals have been analyzed. There was a trend towards a greater average number of postsynaptic cytoplasmic AMPAR per axo-spinous synapses for mice given the 30mg/kg dose compared to the 3mg/kg dose (t-test, $t = 2.339$, $p = 0.05$). In addition, there was a significant negative correlation between ABA2-minus-ABA1 food anticipatory activity (FAA) of the two dose-groups combined and postsynaptic cytoplasmic AMPAR for excitatory synapses of PN ($r^2 = 0.5467$, $p = 0.02$). By contrast, there was no such correlation for GABA-IN. This indicates that those individuals with the strongest suppression of wheel running were the same individuals that exhibited the greatest sequestration of AMPAR near (<1um) but functionally segregated from postsynaptic membranes. This finding fits with a previously proposed idea that suppression of excitatory outflow from PFC to dorsal medial striatum leads to the desirable outcome of reduced wheel running in ABA2 (Santiago et al., 2021, DOI: 10.1093/cercor/bhaa394). Our preliminary findings show that cell-type specific changes in the level and distribution AMPAR contribute to the mechanism that drives the sustained efficacy of the 30mg/kg ketamine.

Disclosures: **B. Xu:** None. **Y. Chen:** None. **C. Carrasco:** None. **R. Temizer:** None. **C.J. Aoki:** None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.30/N7

Topic: G.08. Other Psychiatric Disorders

Support: Vulnerable Brain Project Grant
Baszucki Group Grant
NYU DURF grant
NSF-REU Grant DBI-1950649

Title: Sub-anesthetic ketamine versus ketogenic food in ameliorating activity-based anorexia of adult mice

Authors: *C. AOKI[1,2];
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]Neuroscience Institute, NYU Langone, New York, NY

Abstract: Anorexia nervosa is a mental illness with the highest mortality rate, high relapse rate and no accepted pharmacotherapy. Activity-based anorexia (ABA) is an animal model that captures hallmarks of the illness, including heightened anxiety, voluntary food restriction, hyperactivity, and severe weight loss. These maladaptive behaviors are evoked by combining wheel access with restriction of food access to 2 hrs/day. The maladaptive behavioral phenotypes are replayed when animals undergo repeated cycles of ABA (ABA2, ABA3), simulating relapse. Notably, some individuals are able to curtail these maladaptive behaviors. The objective of this study was to investigate whether ketamine (Ket) or ketogenic food (KG) boosts suppression of the maladaptive behaviors during ABA2 and ABA3.Seventy-seven C57BL6 mice underwent ABA. ABA vulnerability was categorized as severe, based on weight loss ≥20%, food-anticipatory wheel activity (FAA) ≥3.77 km/6 hr and mortality. The first ABA (ABA1) was induced in late adolescence/young adulthood (P52-72). One or two more ABAs (ABA2, ABA3) were imposed, each after 9-10 days of recovery with *ad libitum* food. ABA vulnerability was compared across three groups: (1) Ketx3 injected intraperitoneally (IP) with 30 mg/kg Ket for 3 consecutive days during food restricted days (FR) of ABA2 while fed standard rat pellets (N=13); (2) age-matched CON, fed standard diet without (N=20) or with (N=13) IP vehicle (Vx3) during ABA2; (3) KG, exposed to ketogenic food, only, starting from ≥ 5 days preceding FR, throughout the FR of ABA and during recovery from the FR days (KG-1/2, N=31).Severe weight loss was observed for 100% of CON during ABA3 versus 69% of Ketx3. Severe hyperactivity was prevalent (64%) among CON during ABA2, causing 1 death. None of the Ketx3 died, severe hyperactivity was reduced to 46% during ABA2, and their running per 24 hr was significantly less throughout ABA2 and during ABA3, 10 days post Ket. Further analysis of wheel activity revealed that Ketx3 reduced running significantly during the two hours of food availability acutely (during ABA2) and throughout the FR days of ABA3, >10 days after ket injections and also trended towards reducing running during the light hours. They also ate significantly more during recovery. Remarkably, only 23% of KG-1/2 were severely hyperactive, only 33% lost weight severely and reduction of hunger-evoked hyperactivity was significant for all ABA days. Since KG-1/2's caloric intake was not more than that of CON, the improved weight retention is likely due to reduced hyperactivity.Adults experiencing anorexia nervosa relapse may be helped by Ket and even more by ketogenic food.

Disclosures: C. Aoki: None.

Poster

PSTR041: Hallucinogens: Neural Mechanisms

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.31/N8

Topic: A.07. Developmental Disorders

Title: How do adaptogenic mushrooms impact endosomal trafficking?

Authors: R. HARSHMAN[1], N. SMALL[1], K. ROACH[1], L. GEHNER[1], G. PHILLIPS[1], S. GREGORETTI[1], A. KUNNATHA[1], L. JAMES[1], ***J. L. LARIMORE**[2];
[2]Neurosci. and Philosophy, [1]Agnes Scott Col., Atlanta, GA

Abstract: Endosomal trafficking is necessary for properneuronal morphology as well as receptor trafficking. This study willinvestigate the effects on cellular morphology and endosomal traffickingkinetics of common antipsychotic drugs. The morphology and trafficking proteinlevels will be compared to cells treated with adaptogenic mushrooms. We willuse bright field microscopy to examine morphological changes andimmunocytochemistry to examine any alterations in trafficking kinetics andtrafficking protein markers. Based on initial results, our studies indicatethat adaptogenic mushrooms do not alter trafficking kinetics, but enhanceneurite outgrowth in PC-12 cells. This study enhances our understanding of thecellular mechanisms of adaptogenic mushrooms.

Disclosures: R. Harshman: None. **N. Small:** None. **K. Roach:** None. **L. Gehner:** None. **G. Phillips:** None. **S. Gregoretti:** None. **A. Kunnatha:** None. **L. James:** None. **J.L. Larimore:** None.

Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.01/Web Only

Topic: H.01. Attention

Title: Eccentricity and change blindness

Authors: *C. KOCH;
Psychology, George Fox Univ., Newberg, OR

Abstract: Studies examining the effects of eccentricity on attention have often used spatial frequency, orientation, or simple shapes as the visual stimuli (e.g., Thomas, 1987, Patel, Lewis, and Neider, 2014). Previous research of this type has generally shown reduced attentional processing at increased eccentricities (e.g., Carrasco and Yeshurun, 1998). In this study, change blindness was examined using visual scenes. Images were taken from Le Moan and Pederson (2019). Four versions were created for each of five images. In additional to the original scene, an object within the scene was enlarged to create a foveal (1 deg), parafoveal (4 deg), and peripheral (7 deg) change version. In a given trial, participants were presented with a fixation point (100 msec), an original image (250 msec) followed by a 100 msec ISI before a second image was presented for 250 msec. The second image was either the same as the original (no change) or one of the three altered versions. Participants (n =18) were required to indicate if the second image was changed in any way and generally indicate where the change took place. Participants also provided a confidence rating for their responses. Images were presented randomly across 140 trials. The images appeared briefly to eliminate eye movements thereby limiting attentional

processing to the information immediately available across the retina. However, the brief durations also made the task rather difficult. Nevertheless, participants were better than chance at detecting a change ($p = .003$). However, they were no better than chance at indicating the location of the change. Therefore, the current results suggest that at a minimal level of attentional processing occurs across eccentricities but the details of the attentional processing are limited without saccadic eye movements across the scene. This finding further suggests that oculomotor control plays an important role in providing the visual system with sufficient information to adequately evaluate changes in scene perception (cf., Wollenberg, Hanning, and Duebel, 2020).

Disclosures: C. Koch: None.

Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.02/N9

Topic: H.01. Attention

Support: MR/V003623/1

Title: Causal Roles of Neural Synchrony in Human Cognition

Authors: *M. MELCÓN[1], D. VENIERO[2], J. TRAJKOVIC[3], S. PALVA[4], G. THUT[5]; [1]Univ. of Glasgow, Glasgow, United Kingdom; [2]Sch. of Psychology, Univ. of Nottingham, Nottingham, United Kingdom; [3]Dept. of Cognitive Neurosci., Fac. of Psychology and Neurosci., Maastricht Univ., Maastricht, Netherlands; [4]Neurosci. Ctr., Helsinki Inst. of Life Sci., Univ. of Helsinki, Helsinki, Finland; [5]Ctr. for Cognitive Neuroimaging, Sch. of Psychology and Neurosci., Univ. of Glasgow, Glasgow, United Kingdom

Abstract: Neural synchronization has been described as a key regulatory mechanism for feedback control over feedforward flow of information. In particular, slower frequencies in the alpha/beta bands characterize the feedback signal while feedforward propagation is shaped at gamma rhythm. This has been corroborated in recent studies on the causal role of neural synchrony combining Electroencephalography (EEG) and online Transcranial Magnetic Stimulation (TMS). Our aim was to further test these feedback and forward dynamics in the attentional network in a TMS-EEG experiment stimulating their key nodes: The Frontal Eye Field (FEF, attentional control area), extrastriate cortex (V5, involved in motion processing) and an active control (M1 foot area). Thirty-two volunteers performed in a near threshold visuospatial cueing task, where the feedforward propagation was meant to be enhanced by presenting sine gratings with concentric motion in half of the trials. Participants were asked to covertly shift their attention according to the cue, which could point to the left or right hemifield (80% validity) or instructed not to deploy attention as no targets appeared later. After the cue onset, a single-pulse TMS was applied over FEF, V5 or M1 foot area, always on the right hemisphere in a block design. The cue interval ended with the presentation of a target (10%

catch trials), whose detection and location had to be reported by the participants. Target stimuli were calibrated before the session at 75% individual perception threshold. Preliminary analysis consisted of computing time-frequency amplitude and intertrial phase coherence (ITPC) values in a 1s time window (±500ms around the TMS pulse) in a 2-100Hz frequency-range. Then, to isolate the TMS effect on the neural fingerprints of attention, we contrasted the attentional cue and no-attentional cue condition. Amplitude and ITPC effects were tested for alpha/beta and gamma bands on the time windows before and after the TMS pulse by means of a four-way repeated measures ANOVA (attentional cue x hemisphere x time window x grating presence). Preliminary results show an interaction effect between time window and grating presence: alpha amplitude is reduced after the TMS pulse in trials with grating presentation. Therefore, FEF TMS seems to disrupt the feedback process during spatial attention when feedforward propagation has been enhanced. Further analyses including the control stimulation sites will elucidate the state-dependency of TMS-effect and the role of brain oscillations in information flow.

Disclosures: **M. Melcón:** None. **D. Veniero:** None. **J. Trajkovic:** None. **S. Palva:** None. **G. Thut:** None.

Poster

PSTR042: Mechanisms of Attention in Human

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Topic: H.01. Attention

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DFG HE8329/2-1
Hertie Foundation, Network for Excellence in Clinical Neuroscience
1 PO MH109429
2 R01 NS021135

Title: The Aperiodic Temporal Structure of Human Attention

Authors: *I. RAPOSO[1,2], I. C. FIEBELKORN[3], J. LIN[4], J. PARVIZI[5], S. KASTNER[6], R. T. KNIGHT[7], A. BRESKA[8], R. F. HELFRICH[9];
[1]Human Intracranial Cognitive Neurophysiol., Hertie Inst. for Clin. Brain Res., Tuebingen, Germany; [2]Intl. Max Planck Res. Sch., Tuebingen, Germany; [3]Univ. of Rochester, Rochester, NY, ; [4]Univ. of California, Irvine, Irvine, CA, ; [5]Stanford Univ. Sch. of Med., Stanford, CA, ; [6]Princeton Univ., Princeton, NJ, ; [7]Psychology and Neurosci., UC Berkeley, el cerrito, CA; [8]Dynamic Cognition, Max-Planck Inst. for Biol. Cybernetics, Tuebingen, Germany, Tuebingen, Germany; [9]Hertie Inst. for Clin. Brain Res., Univ. of Tuebingen, Tuebingen, Germany

Abstract: Attention samples visual space sequentially to enhance behaviorally-relevant sensory representations. While traditionally conceptualized as a static continuous spotlight, contemporary

models of attention now highlight its discrete nature. But which neural mechanisms govern the temporally precise allocation of attention? Periodic brain activity as exemplified by neuronal oscillations as well as aperiodic temporal structure in the form of intrinsic neural timescales have been suggested to orchestrate the attentional sampling process in space and time. However, both mechanisms have been largely studied in isolation. To date, it remains unclear whether periodic and aperiodic temporal structure reflects dissociable neural mechanisms. Here, we combined computational simulations with a multimodal approach that encompassed five experiments, and three different variants of classic spatial attention paradigms, to dissociate aperiodic from oscillatory-based sampling. Converging evidence across behavior as well as scalp and intracranial electroencephalography (EEG) revealed that periodic and aperiodic temporal regularities can theoretically and experimentally be dissociated. Our results extend the rhythmic sampling framework of attention by demonstrating that aperiodic neural timescales predict behavior in a spatially-, context- and demand-dependent manner: Aperiodic timescales increased from sensory to association cortex, decreased during sensory processing or action execution and were prolonged with increasing behavioral demands. In sum, these results reveal that multiple, concurrent temporal regularities govern the attentional sampling process.

Disclosures: **I. Raposo:** None. **R.T. Knight:** None. **A. Breska:** None. **R.F. Helfrich:** None.

Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.04/N11

Topic: H.01. Attention

Support: GR531425

Title: Does rhythmic, attention-related sampling modulate the likelihood of distractibility?

Authors: *Y. DING[1], Z. V. REDDING[2], I. C. FIEBELKORN[3];
[1]Univ. of rochester, Rochester, NY; [2]Univ. of Rochester Med. Ctr., Rochester, NY; [3]Neurosci., Univ. of Rochester, Rochester, NY

Abstract: The metaphorical spotlight of spatial attention seems to dim about 4-6 times per second. Here, we tested whether this dimming at the presently attended location is associated with a periodic increase in distractibility. We simultaneously recorded EEG and gaze position, while human participants completed a Posner-like spatial-cueing task. On each trial, a peripheral cue indicated the most likely location for a subsequent, low-contrast visual target. On half of the trials, the target co-occurred with a salient distractor (i.e., a task-irrelevant stimulus that occurred away from potential target locations). The behavioral results show that the spatially informative cue improved performance by speeding responses and increasing detection, while the co-occurrence of a distractor impaired performance by slowing responses and decreasing detection. The spatial cue further induced an attention-related, increase in sustained neural activity during

the cue-target delay, measured by the difference between the contralateral and ipsilateral electrodes over parietal-occipital areas. This sustained neural activity, however, only predicted response speeds when there was no distractor. In comparison, faster responses on distractor-present trials were associated with a lower-amplitude distractor-evoked potential (i.e., ERP). To address our main hypothesis, we will examine whether behavioral measures and eye movements are correlated with the phase and power of frequency-specific, pre-target neural activity. Specifically, we will examine whether: (1) pre-target phase (e.g., theta-band activity) is correlated with response times, accuracy, and microsaccades, (2) whether the spatial distribution on the scalp of behaviorally relevant neural activity varies across these various behavioral measures, and (3) whether rhythmic neural activity is correlated with the amplitude of attention-related ERP components, such as distractor-evoked responses.

Disclosures: Y. Ding: None. **Z.V. Redding:** None. **I.C. Fiebelkorn:** None.

Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.05/N12

Topic: H.01. Attention

Support: NSF Grant

Title: Both Target and Distractor are Sampled Rhythmically in a Motion Detection Task

Authors: *C. XIONG[1], K. BO[2], N. M. PETRO[1], A. KEIL[3], M. DING[3];
[1]Univ. of Florida, Gainesville, FL; [2]Dept. of Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [3]Univ. Florida, Gainesville, FL

Abstract: It has been shown that the visual system samples the attended information rhythmically. Does rhythmic sampling also apply to distracting information? How do attended information and distracting information compete temporally for neural representations? We recorded electroencephalography from participants who detected instances of coherent motion in a random dot kinematogram (RDK) (primary task) overlayed on different categories (pleasant, unpleasant, and neutral) of affective images from the IAPS library (distractor). The RDK was flicked at 4.29 Hz whereas the IAPS pictures at 6 Hz. From the SSVEP time series, the time course of the power at 4.29 Hz was extracted in a moving window approach, and its fluctuation was taken to index the temporal dynamics of attended information processing. The time course of the power at 6Hz was similarly extracted and support vector machine (SVM) was applied to decode different categories of affective images with the resulting fluctuating decoding accuracy taken to index the temporal dynamics of distracting information processing. We found that (1) both the 4.29 Hz power time course and the 6 Hz decoding accuracy time course exhibited rhythmicity at 1 Hz and (2) the phase difference between the two rhythmic time courses predicted task performance, i.e., phase difference close to pi corresponded to a higher rate of

coherent motion detection whereas phase difference close to 0 corresponded to a lower rate of coherence motion detection. These results suggest that (1) both attended and distracting information were sampled rhythmically and (2) alternating the sampling between target and distractor reduces the adverse impact of distractor.

Disclosures: C. Xiong: None. **K. Bo:** None. **N.M. Petro:** None. **A. Keil:** None. **M. Ding:** None.

Poster

PSTR042: Mechanisms of Attention in Human

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Program #/Poster #: PSTR042.06/N13

Topic: H.01. Attention

Support: Boston University Startup Grant

Title: Temporal normalization incentivizes attentional tradeoffs across time

Authors: *A. CHAPMAN, R. N. DENISON;
Boston Univ., Boston, MA

Abstract: Motivation: Temporal attention prioritizes stimuli at relevant points in time, resulting in increased perceptual sensitivity to attended stimuli but decreased sensitivity to stimuli presented at other times. These tradeoffs across time induced by temporal attention mirror tradeoffs in spatial and feature-based attention. One explanation for such tradeoffs is competition for a limited attentional resource: allocation of attention to one stimulus reduces what remains for others. In contrast, normalization models argue that the effects of attention can be understood by examining how attention shifts the balance of excitation and suppression among competing stimuli. To date, only the attentional resource account has been proposed for temporal attention. Here we investigated whether normalization can capture attentional tradeoffs across time without requiring an explicit attentional resource. Methods: We implemented temporal normalization in a recurrent neural network model, previously used to capture temporal dynamics in perception and attention (Denison, Carrasco, & Heeger, 2021). Temporal receptive fields caused excitatory and suppressive drives to depend on the input at both current and previous timepoints. We simulated the model's response to a sequence of two target orientations with varied stimulus onset asynchrony (SOA), and independently modulated the gain applied to each stimulus to simulate different attention cueing conditions. Results: Under a range of parameter settings, temporal normalization reproduced bidirectional attentional tradeoffs across time. To determine the optimal allocation of attention under temporal normalization, we calculated the expected model response under different attention conditions (T1 cued, T2 cued, or neutral cue) as a weighted sum of the response to each stimulus. At short SOAs, the highest expected response was obtained when gain was maximal to the cued stimulus and minimal to the uncued stimulus. When SOAs were longer, however, responses to each stimulus were less overlapping, and the

model shifted to prefer maximum gain to both stimuli. Under neutral cues, the highest response was with maximum gain to both stimuli regardless of SOA. Conclusions: In our simulations, temporal normalization incentivized attention to the stimulus at the cued time. This effect was specific to short SOAs where temporal receptive fields of both stimuli were highly overlapping. Our findings suggest that attentional tradeoffs across time do not require an explicit resource limit, and that the interaction of attention and temporal normalization could shift the balance of processing towards relevant points in time.

Disclosures: A. Chapman: None. **R.N. Denison:** None.

Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.07/N14

Topic: H.01. Attention

Support: NIMH Silvio O. Conte Grant

Title: Detecting when the mind wanders off task without self-report using intracranial EEG and eye movements

Authors: *C. B. CHESEBROUGH[1], M. NENTWICH[2], S. BICKEL[3];
[1]Feinstein Inst. for Biomed. Res., Manhasset, NY; [2]The Feinstein Inst. for Med. Res., New York, NY; [3]Neurosurg. - Neurol., Feinstein Inst., Manhasset, NY

Abstract: Even when engaged in a task requiring externally-oriented attention, our attention naturally alternates between being focused on external stimuli and our own thoughts and bodily sensations. In the present investigation, we use intracranial EEG recordings and eye movements to detect naturally occurring states of internally vs externally-oriented attention during continuous movie watching in order to probe the mechanisms by which the brain spontaneously switches between attentional states. We analyzed recordings from $N = 15$ patients undergoing treatment for drug-resistant epilepsy. Whereas most previous research on MW and TUT depends on subjects to self-report their attentional state, here we rely on eye behaviors including gaze position, saccade rate, and angle of eye vergence to detect periods during movie watching when patients' attention was likely engaged or disengaged from external stimuli. The most consistent electrophysiological signature of mind-wandering and task-unrelated thought is increased alpha power in the brain's sensory regions, which suggests that internally-directed attention involves attenuation of external information. We compared alpha power between states of hypothesized internally and externally-oriented attention in relevant parcellations (e.g. inferior parietal, lateral occipital, transverse temporal gyrus) and found significant differences in alpha power between internal and external states. Such differences were not observed in control regions. Though the phenomena of mind wandering (MW) and task-unrelated thought (TUT) have received increased interest from researchers in recent years, the mechanisms by which the brain switches between

externally and internally-oriented attention are still poorly understood. Here, we demonstrate that spontaneously occurring attention states can be approximated using eye movements and intracranial recordings without the need for self-report. Future work will continue to disentangle the nature and mechanisms of spontaneous attentional switches in the brain at finer-grained levels of analysis and in a variety of tasks.

Disclosures: C.B. Chesebrough: None. **M. Nentwich:** None. **S. Bickel:** None.

Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.08/N15

Topic: H.01. Attention

Title: Thalamocortical Signatures of Attention Processing in Rapid Serial Visual Presentation

Authors: *A. R. KIMATA[1], S. CHAMARTHI[2], T. WATANABE[3], W. F. ASAAD[4]; [1]Dept. of Neurosci., [2]Brown Univ., Providence, RI; [3]Cognitive, Linguistic, and Psychological Sci., Brown Univ., Westwood, MA; [4]Neurosurg., Brown Univ., Westwood, RI

Abstract: Rapidly processing the visual world is a skill that requires people to deploy attention to detect relevant, often fleeting information. Prior work has suggested that dynamic changes in cortical and subcortical oscillations, particularly in the theta (3-8 Hz) and alpha (9-12 Hz) bands, may be critical to attention processing, yet the precise direction of these changes remains unclear. Additionally, there is some evidence that the middle frontal gyrus may be an important region for reorienting endogenous attentional processes and integrating activity from the dorsal and ventral visual streams. In the present study, we employed a unique single-stream rapid serial visual presentation (RSVP) task previously developed by our group to investigate the oscillatory changes associated with activating attention to a novel target in the context of lag-1 sparing. Epilepsy patients with stereotactic electroencephalography (SEEG) electrodes were asked to perform the RSVP task, and behavioral performance and continuous intracranial local field potentials were recorded for the duration of the task period. Analysis of imaging data confirmed the location of SEEG electrodes in patient-specific anatomical space, including contacts in thalamus, inferior frontal gyrus, middle frontal gyrus, hippocampus, and entorhinal cortex. Our analyses demonstrated a decrease in thalamic theta power at the time of cue (“T1”) and target (“T2”) presentation within the RSVP stream on trials where T2 was correctly identified compared to trials where T2 was missed. Additionally, the middle frontal gyrus (MFG) showed a decrease in theta and increase in alpha power at T2 presentation. These changes were associated with behavioral performance accuracy greater than chance level. Phase-locking analysis revealed significantly greater theta phase-locking between the thalamus and pre-frontal cortical (PFC) regions at cue presentation for trials where subjects performed correctly *vs.* incorrectly ($p=0.042$). These findings suggest a potential role of thalamocortical oscillations in the deployment and adaptation of attentional resources under challenging attentional constraints.

Disclosures: **A.R. Kimata:** None. **S. Chamarthi:** None. **T. Watanabe:** None. **W.F. Asaad:** Other; U01 NS121616 (PI: Z. Williams) and by the Norman Prince Neurosciences Institute (Providence, RI).

Poster

PSTR042: Mechanisms of Attention in Human

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NINDS Grant 2 R01 NS021135

Title: High-frequency burst dynamics support attentional information routing in the human brain

Authors: *K. BANAIE BOROUJENI[1,2], R. F. HELFRICH[3], I. C. FIEBELKORN[4], J. LIN[5], N. BENTLEY[6], R. T. KNIGHT[7], S. KASTNER[8];
[1]Princeton Univ., Princeton, NJ; [2]Princeton Neuroscience Institute, Princeton University, Princeton, NJ; [3]Hertie Inst. for Clin. Brain Res., Univ. of Tuebingen, Tuebingen, Germany; [4]Neurosci., Univ. of Rochester, Rochester, NY; [5]Dept. of Neurol., Univ. of California, Irvine, Irvine, CA; [6]Neurosurg., Univ. of Alabama at Birmingham, Birmingham, AL; [7]Psychology and Neurosci., UC Berkeley, el cerrito, CA; [8]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Prioritizing sensory attention cues for guiding upcoming actions requires coordination of neural activity on fast timescales across large-scale networks distributed across distant brain areas. This fast coordination allows information to be routed selectively from sensory to higher level executive brain networks. However, the mechanisms by which these fast neural dynamics emerge and enable information routing within these networks are not well understood. Using spiking neural network modeling and human intracranial electrophysiology (iEEG), we show that high-frequency activity bursts (65-115 Hz, HFAb) can serve as discrete packets of information facilitating such fast and long-range communication. First, we modeled two inter-connected networks of neurons and fed these networks different levels of input coherence. We found that HFAbs emerge as coherent activations of population of neurons. HFAb events were synchronized to low frequency field potentials and coordinated between different networks through shared external drives or inter-network connections. Our modeling results set the stage to explore HFAbs in iEEG data from human epilepsy patients performing spatial attention tasks. In these tasks, patients were cued either exogenously or endogenously to a spatial location to

detect visual targets. HFAbs were more frequent in occipital and parietal cortices following a cue while they were more widely distributed across brain regions following target events. Next, we calculated the number of HFAb events as a function of time (i.e., rate) for each electrode. On a trial-by-trial basis, HFAb rates measured within 500 ms after sensory cues predicted successful detection of upcoming targets (binomial test, $P<0.001$). To investigate the spatiotemporal coordination of these HFAbs, we examined correlations of HFAbs between pairs of electrodes. HFAbs were coordinated brain-wide on a low frequency theta rhythm. We clustered electrodes in each subject using network-level HFAb coordination outside of the cue-to-response period to avoid any event-triggered HFAb activations. The baseline coordination of HFAbs in brain networks revealed functionally specialized subnetworks that were activated in response to cue and target events. These cue and target subnetworks showed distinct topographical and temporal organization, with cue subnetworks preceding information in target subnetworks following target onset. In summary, our findings provide new insight into how sensory cue information is routed in large-scale brain networks to facilitate upcoming target detection.

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Poster

PSTR042: Mechanisms of Attention in Human

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Program #/Poster #: PSTR042.10/N17

Topic: H.01. Attention

Support: NIMH Grant P50MH132642
NIMH Grant R01MH064043

Title: Endogenous attentional sampling under spatial uncertainty

Authors: *X. LIU[1], M. J. ARCARO[2], M.-L. G. TRAN[3], H. J. ALITTO[3], W. USREY[4], S. KASTNER[5,6];
[1]Psychology, Princeton Univ., PRINCETON, NJ; [2]Psychology, Univ. of Pennsylvania, Philadelphia, PA; [3]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA; [4]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA; [5]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [6]Psychology, Princeton University, Princeton, NJ

Abstract: Theories of rhythmic perception propose that the environment is sampled in cycles, with alternating states of enhanced or diminished perceptual sensitivity at an attended location. These cycles involve periodic adjustments in functional communication between higher order thalamic nuclei, such as pulvinar (PUL) and mediodorsal nucleus (MD), and the frontoparietal networks (FPN) (Fiebelkorn et al., 2019). Previous research has shown robust rhythmic sampling with exogenous spatial cues that automatically direct attention (e.g., Fiebelkorn et al., 2013). However, it remains unclear whether the same applies to endogenous, voluntary attention, which

relies on different neural mechanisms, and how spatial uncertainty affects the rhythmic process. To investigate, we conducted an experiment that combined elements of perceptual decision making and spatial attention tasks. In each trial, participants maintained central fixation while viewing two gratings displayed at either side in their periphery. A centrally presented cloud of red and blue dots served as a cue, with the red-to-blue ratio of the colored dots indicating the location of an upcoming target with 80% validity. Spatial uncertainty was manipulated by varying the ratio of the colored dots. After cue offset, the target, a brief near-threshold orientation change, appeared at one of the two grating locations at a randomly selected cue-target interval (CTI) from 300 to 1100 ms. After participants responded to the target, they indicated their perceptual uncertainty toward the cue with a five-point confidence rating. We observed a significant endogenous attention effect, where target detection performance (accuracy and reaction time) was better at the cued vs. uncued location. This effect diminished with increased spatial and perceptual uncertainty. When analyzing performance as a function of the CTI, preliminary results show a strong attention rhythm in the theta band in all uncertainty conditions and an anti-phase relationship between cued and uncued locations. This finding supports our hypothesis that endogenous attentional sampling is a rhythmic process. We are adapting the task for fMRI to test the role of thalamocortical connectivity in modulating attention allocation under uncertainty. We predict that 1) PUL integrates signals across the FPN to facilitate attention allocation, with a decreased activity as uncertainty increases reflecting perceptual confidence, and 2) MD-PFC activity increases to reflect increasing cognitive control under higher uncertainty.

Disclosures: **X. Liu:** None. **M.J. Arcaro:** None. **M.G. Tran:** None. **H.J. Alitto:** None. **W. Usrey:** None. **S. Kastner:** None.

Poster

PSTR042: Mechanisms of Attention in Human

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Program #/Poster #: PSTR042.11/N18

Topic: H.01. Attention

Support: P50MH132642
P30 EY012576

Title: Endogenous and exogenous influences on spatial attention

Authors: *M.-L. G. TRAN[1], H. J. ALITTO[1], D. J. LASKY[1], X. LIU[2], M. J. ARCARO[3], S. KASTNER[2], W. USREY[1];
[1]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA; [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [3]Psychology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Higher order cognitive and executive functions are critically dependent on cortical processing. While the flow of information through the cortex is often thought of as occurring

directly through cortico-cortical connections, every area of the cortex is uniquely and reciprocally connected with a subset of thalamic nuclei. These dense and omnipresent, back and forth projections between the thalamus and cortex provide an alternative route for the flow of information through the cortex: transthalamic pathways. Despite the intricate and inseparable relationship between the thalamus and cortex, the role of transthalamic pathways in higher order cognitive and executive functioning remain unknown. A primary goal of our NIH Conte Center, *the Cognitive Thalamus*, is to develop a better understanding of information processing through transthalamic pathways and how thalamic mechanisms contribute to cognitive and executive functioning. As a first step towards this goal, we explored spatial attention and its dependence on top-down perceptual confidence and bottom-up perceptual distractors using a human psychophysics experiment. Our aim was to understand the dynamics of the task and how endogenous and exogenous mechanisms interact to influence psychophysical performance, with an eye towards optimizing the task for future studies involving neural recording in primates. In the experiment, subjects were shown a dot cloud composed of a variable mixture of red and green dots, followed by a pair of visual stimuli. Each stimulus was surrounded by visual distractors and either a red or green square. The percentage of red vs green dots indicated to the subject which grating was likely to change contrast (95% valid). Subjects were tasked with responding if a contrast change occurred (50% of trials) and withholding a response if no contrast change occurred (50% of trials). Our analysis emphasized the interactions of exogenous and endogenous cues on response accuracy and latency through the modulation of the perceptual uncertainty of the dot cloud and the perceptual salience of the visual distractors. This work is also part of a larger investigation into oscillations in behavioral performance that occur in the range of both theta (3-6 Hz) and alpha oscillations (8-12 Hz), which likely represents a behavioral signature of an underlying neural oscillation. Overall, this experiment has provided insight into the relationship between endogenous and exogenous contributions to attention and provided the framework for future electrophysiological experiments.

Disclosures: **M.G. Tran:** None. **H.J. Alitto:** None. **D.J. Lasky:** None. **X. Liu:** None. **M.J. Arcaro:** None. **S. Kastner:** None. **W. Usrey:** None.

Poster

PSTR042: Mechanisms of Attention in Human

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Program #/Poster #: PSTR042.12/N19

Topic: H.01. Attention

Support: UWM Research Growth Initiative Award 101x388

Title: Voxel-wise quantification of attention-based saccade planning

Authors: *W. E. HUDDLESTON[1], M. J. PENNING[1], A. S. GREENBERG[2], E. A. DEYOE[3]; [1]Sch. of Rehabil. Sci. & Technol., Univ. of Wisconsin - Milwaukee, Milwaukee, WI; [2]Biomed. Engin., [3]Dept. of Radiology, Med. Col. of Wisconsin, Milwaukee, WI

Abstract: The topography of saccade targets has long been established as being represented in human posterior parietal cortex by our group and others. However, the role of attentional modulation of such a map has not been fully elucidated. In vision, attentional modulation can be retinotopically specific and directed selectively to behaviorally relevant locations or objects in space. Yet, spatial vision is not the only system modulated by attention. One can readily attend to a variety of sensory features as well as eye and body movements. Lacking, however, is a detailed comparison of the neural mechanisms across modalities. The primary aim of this study was to compare voxel-wise saccade motor fields (SMF) and motor attention receptive fields (MARF) in parietal cortex using an attentional drift experimental design and attention field mapping as described in Puckett and DeYoe (2017). Participants (n = 44, 9 male, aged 20-54 (mean = 32 years)) performed two tasks while undergoing functional magnetic resonance imaging at 3T. In a first task, participants made saccadic eye movements between two diametrically opposed targets rotating clockwise every 8 seconds (a full rotation taking 48 seconds and 4 rotations completed every run. Participants completed 4 runs). From these data we calculated SMFs on a voxelwise basis (3 x 3 x 3 mm). In a second task, participants selectively attended to a centrally presented RSVP stream surrounded by 24 static targets (8 degree radius). Every 4 seconds, a letter 'N' appeared in the RSVP to cue participants to prepare a saccade to the next target clockwise, creating a drifting focus of motor attention (i.e. saccade intention) across the saccade trajectory map. Participants delayed saccade execution until a rarely presented 'X' appeared in the central RSVP stream (4-5 times per run, for a total of 19 saccades to unique targets across the 4 runs). In significantly active voxels within the parietal region of interest (ROI), the signal during the attentional drift task showed a significantly better fit (correlation coefficient; $t(33) = 4.691$, $p = 0.00005$) and SNR ($t(33) = 2.080$, $p = 0.046$ than for the saccade task. However, the SMFs had smaller field sizes ($t(33) = 2.910$, $p = 0.006$). Interestingly, the anatomical location of active voxels differed significantly between the two tasks, in at least some of the participants, which is inconsistent with the pattern noted in spatial vision where active voxels for retinotopy and visuospatial attention overlapped in parietal cortex. The ability to quantify MARFs using our approach highlights the importance of using a common methodologies across modalities to test universality or uniqueness of attentional mechanisms.

Disclosures: W.E. Huddleston: None. **M.J. Penning:** None. **A.S. Greenberg:** None. **E.A. DeYoe:** None.

Poster

PSTR042: Mechanisms of Attention in Human

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Topic: H.01. Attention

Support: University of Wisconsin Milwaukee Research Growth Initiative Award

Title: Are neuronal mechanisms of attention universal across human sensory and motor brain maps?

Authors: *E. DEYOE[1], A. S. GREENBERG[2], W. E. HUDDLESTON[3];
[1]Radiology, [2]Biomed. Engin., Med. Col. of Wisconsin, Milwaukee, WI; [3]Rehabil. Sci. & Technol., Univ. of Wisconsin - Milwaukee, Milwaukee, WI

Abstract: One's experience of shifting attention from the color, to the smell, to the act of picking a flower seems like a unitary process applied, at will, to one modality after another. Yet, the distinct and separable experiences of sight vs smell vs movement suggest that the neural mechanisms of attention may be uniquely designed for each modality. While there is a long history of studies focused on visual attention, assessing universality is particularly difficult due to a paucity of existing cross-modal studies and neurophysiological methods that can be applied equally well across disparate modalities and submodalities. In the theoretical/conceptual treatise presented here, we outline some of the conceptual and methodological issues related to this problem and present an instructive example of an experimental approach that can be applied widely throughout the human brain to permit detailed, quantitative comparisons of attentional mechanisms across modalities. First, we identify certain aspects of attention-related neural function that can be fruitfully compared across modalities. These include the characterization of neuronal maps of task-relevant information and the extended patterns of attentional modulation (attentional fields) impressed upon them to select the requisite information. We then consider what types of neurophysiological measurements can be used across modalities to test universality, thereby introducing the concept of population attentional receptive fields (pARFs) that are an extension of the widely accepted notion of sensory population receptive fields (pRFs). We then outline an fMRI-based paradigm (Attentional Drift Design, ADD) to characterize and quantify pARFs and the fields of attentional modulation that extend across many if not all functional areas of the human cerebral cortex. We then describe how this approach can be applied across modalities to test universality. Finally to provide a more concrete anatomical/neural context for these concepts, we outline a speculative neuronal substrate and discuss how the proposed attentional mechanisms relate to previous work in the field. Our ultimate goal is to spur efforts across disciplines to provide a large and varied database of empirical observations that will either support the notion of a universal neural substrate for attention or more clearly identify the degree to which attentional mechanisms are specialized for each modality. Additional studies addressing potentially universal attentional mechanisms in the saccadic motor system and in various submodalities of vision are presented at this meeting by our collaborative group (See Huddleston, Greenberg authors).

Disclosures: E. DeYoe: None. **A.S. Greenberg:** None. **W.E. Huddleston:** None.

Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.14/N21

Topic: H.01. Attention

Support: NCATS CTSA ULT1TR001436

Title: Sleep Duration and Variability Over a Two-Week Period Affect Attentional Control Performance

Authors: *B. GREINER[1], G. GURARIY[2], A. S. GREENBERG[3];
[1]Dept. of Biophysics, Med. Col. of Wisconsin Neurosci. Doctoral Program, Milwaukee, WI;
[2]Dept. of Biomed. Engin., [3]Biomed. Engin., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: The ability to stay alert, orient your attention, and filter out irrelevant or distracting information is key to effective task completion. Lifestyle factors, such as sleep, are known to impact cognitive performance. However, studies tend to focus on instances of total sleep deprivation rather than the impacts of shortened sleep duration (i.e. less than seven hours of sleep). Previous work has also focused on more generalized cognitive dysfunction, rather than specific mechanisms or subprocesses. Here, we aimed to determine the impacts of consistently shortened sleep and sleep pattern variability on the three subprocesses of attentional control as measured via Attention Network Test (ANT; Fan et al. 2002): alerting, orienting, and executive control (i.e. distractor filtering). Participants were loaned an iPad containing our ANT app to track attentional performance across 42 sessions over a 12-day period. Prior to the first session of each day, participants were asked to report the previous night's sleep duration. A two-sample t-test revealed that individuals who reported consistently shortened sleep durations (less than seven hours) showed poorer average orienting performance over the two-week period ($p = 0.0230$; $N_1=23$, $N_2=22$). Average sleep duration did not significantly impact performance on the other attentional control subprocesses. Interestingly, we found that all participants showed improved distractor filtering ($p < 0.001$, $N=45$) as a result of repeated ANT task completion and those with consistently shortened sleep durations had a slower rate of improvement compared to those consistently getting seven to nine hours of sleep a night. Additionally, this improvement is related to the variability in sleep duration ($p = 0.0395$), where more variability led to greater filtering improvement. These results begin to uncover the specific attention mechanisms affected by sleep duration and inconsistency. Further analyses include assessing the impact of sleep quality on attentional control performance and examining changes in attentional control fMRI activation patterns between the first and last day of the study.

Disclosures: B. Greiner: None. **G. Gurariy:** None. **A.S. Greenberg:** None.

Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.15/N22

Topic: H.01. Attention

Support: NSF Grant BCS-2122866

Title: Multivariate pattern analysis indexes non-cued shifts of object-based attention, revealing activation differences between cued and non-cued shifts

Authors: *D. H. HUGHES[1,2], A. S. GREENBERG[1,2];
[1]Med. Col. of Wisconsin, Milwaukee, WI; [2]Marquette Univ., Milwaukee, WI

Abstract: Multivariate pattern analysis can classify neural activations to track fluctuations in attentional states (Greenberg et al., 2010). Our lab extended these methods to index non-cued shifts of spatial attention, revealing earlier activation in a subset of attentional control regions for non-cued relative to cued shifts (Gmeindl et al., 2016). Based on these previous findings, we hypothesized that non-cued shifts of object-based attention (OBA) could be indexed, revealing a subset of attentional control regions exhibiting differential activation for cued versus non-cued OBA shifts. To test this, we recruited 17 healthy adults who completed six task runs during fMRI with each run including both a cued and a non-cued block. The task was to detect a specific face or house target among a rapid serial visual presentation (RSVP) of overlapping face and house images. A thin colored frame provided cues to shift/hold during cued blocks, but not during non-cued blocks (subjects were instructed to shift voluntarily approximately 2-3 times/min). A classifier was trained on cued blocks (via leave-one-run-out cross-validation) to estimate the probability that a subject was attending to faces or houses during a given RSVP frame. The classifier was then applied to both the cued and non-cued block from the testing run, resulting in a probability time course for each block. Time courses remained stable at either extreme (attend face; attend house) with occasional, rapid changes between extremes. Shifts were indexed at the onset of high rate of change moments, and event-related averages time-locked to these indices were extracted from ROIs grown from our previous results (Gmeindl et al., 2016). Activation in left inferior parietal lobule (IPL), precentral gyrus (PrCG), precuneus (PreC), basal ganglia (BG), and superior parietal lobule (SPL) as well as right dorsal anterior cingulate cortex (dACC), IPL, middle frontal gyrus (MFG), and supramarginal gyrus (SMG) were submitted to ANOVAs with the within-subject factors of cue condition (cued; non-cued) and time (± 5 TRs). Preliminary results showed that there was a significant effect of time in left PreC ($p < .001$), and right MFG ($p = .022$), dACC ($p < .001$), and IPL ($p = .036$). The main effect of cue condition was significant in left PreC ($p = .042$), SPL ($p = .030$), and IPL ($p = .003$) and marginally significant in left BG ($p = .086$). The interaction was significant in left IPL ($p < .001$) and marginally significant in left PrCG ($p = .076$). Our initial results demonstrate that non-cued shifts of OBA can be reliably indexed, and a subset of attentional control regions are differentially affected by the presence of shift instructions.

Disclosures: D.H. Hughes: None. **A.S. Greenberg:** None.

Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.16/N23

Topic: H.01. Attention

Support: NSF Grant SBE 2122866

Title: Psychophysical Reverse Correlation Reveals How Objects Are Perceived During Occlusion

Authors: *E. J. DUWELL, A. S. GREENBERG;
Biomed. Engin., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Attention plays an integral role in many aspects of our visual perception and cognition. One counter-intuitive domain in which attention has been implicated is "object grouping," or the perceptual grouping of visual features into objects. Object grouping is influenced by both top-down and bottom-up factors. Many bottom-up gestalt grouping principles have been previously established which cue the visual system to group portions of the visual scene as part of a shared object. However, less work has been done to compare the strength of these grouping cues relative to one another or potential interactions between them. To address this, we developed a behavioral paradigm to compare the effects of various object grouping cues using the Psychophysical Reverse Correlation (PRC) method. On each trial, subjects viewed a pair of rectangular objects with noise overlaid. The objects were angled 45 degrees to either the right or left. On some trials, portions of the objects were occluded, while on other trials the objects were un-occluded. On all trials the subjects' task was to indicate whether the objects were angled right or left. We manipulated three well-known cues across separate experiments: luminance similarity, texture similarity, and common region. In the luminance version, objects were grouped by similarity in luminance relative to the gray background. In the texture version, objects were grouped by similarity in the scale of checkerboard textures. In the common region version, objects were grouped by encircling one with a thin boundary line of varying luminance relative to the background. In each experiment, we combined the noise frames from the correct and incorrect trials in each condition (right and left) to form a classification image (CI). Interestingly, CIs generated from trials in which the objects were occluded suggest that occluded regions still play a role in performing the task. This effect varied across grouping cues. Differences in signal amplitude within these occluded regions and general patterns in the CI images allow us to quantitatively compare the relative strength of the respective object grouping cues. In the future, we will use this method to compare additional object grouping cues and the interactions with attentional processes.

Disclosures: E.J. Duwell: None. **A.S. Greenberg:** None.

Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.17/N24

Topic: H.01. Attention

Support: Cochlear America, Inc.

Title: Evidence of Compensatory Neural Mechanisms in Age-Related Hearing Loss and Cognitive Decline

Authors: G. GURARIY[1], S. ZIADEH[1], S. MLEZIVA[2], K. KOZLOWSKI[2], S. WALSH[2], M. HARRIS[2], ***A. S. GREENBERG**[1];
[1]Biomed. Engin., [2]Otolaryngology & Communication Sci., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: The prevalence of age-related hearing loss (ARHL) is growing, presenting a significant public health challenge amid an aging population. A well-supported correlation exists between ARHL and cognitive decline, as indicated by numerous epidemiological studies. Two main theories attempt to explain this correlation. The sensory deprivation hypothesis suggests that reduced sensory input leads to potentially irreversible brain changes. Conversely, the information degradation hypothesis argues that noisy auditory signals require more cognitive resources, detracting from other mental functions; however, this cognitive decline may be reversible if auditory capabilities are restored. To further investigate how ARHL impacts cognitive function, we conducted a study with patients eligible for cochlear implant surgery who had not yet received the implant (PreCI group), alongside a control group with normal hearing. We utilized the N-back task and Attention Network Test (ANT), cognitive assessment tools that measure visual working memory and attentional control, respectively. Additionally, participants performed these tasks during fMRI to track brain activity. Behavioral results showed no significant differences between the PreCI and control groups in either task, indicating no overt cognitive decline in the PreCI group based on these behavioral tests. However, fMRI data revealed that, during the N-back task, the PreCI group exhibited significantly increased activation in the parietal cortex in the more challenging N=2 condition compared to the N=1 condition. This enhanced neural activity suggests compensatory mechanisms, where attentional resources may be reallocated to maintain cognitive performance. These findings highlight the intricate dynamics between age-related hearing loss, cognitive decline, and the brain's compensatory responses, emphasizing the possible role of attention in moderating the impact of cognitive deficits.

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Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.18/N25

Topic: H.01. Attention

Support: Greater Milwaukee Foundation 20162470

Title: Exogenous shifts of spatial attention operate at a finer resolution than endogenous shifts regardless of stimulus size and spacing

Authors: *C. REYNOLDS[1], A. S. GREENBERG[2];
[1]Psychology, Univ. of Wisconsin Milwaukee, Milwaukee, WI; [2]Biomed. Engin., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Shifts of visuospatial selective attention are limited in spatial resolution (i.e., the required spacing surrounding a target for successful selection; Intriligator & Cavanagh, 2001). Previous research on attention resolution has focused on endogenous selection, but exogenous resolution has been unexplored. Across four experiments we measured the resolution of exogenous shifts of visuospatial attention at two different eccentricities by quantifying the minimum spacing needed for individuals to isolate and select a peripheral target among nearby distractors. Concurrently, we evaluated if exogenous selection operates at a finer resolution than endogenous selection. Participants viewed a circular array of equally spaced, luminance-matched colored disks at 10° (Experiments 1, 2, 3) or 7.5° eccentricity (Experiment 4) on a median gray background with a single white RSVP stream at fixation. The size of the peripheral colored disks was scaled with eccentricity to conserve inter-disk spacing (at 10° eccentricity, diameters 1°, 0.75°, and 0.5°, respectively; and at 7.5° eccentricity, 0.56° diameter). Subjects monitored RSVP items for target digits and responded via button press. Simultaneously, on each trial a black dot briefly (60 msec) appeared (among the peripheral colored disks) which exogenously captured attention. After each trial, participants selected the color corresponding to the location nearest to which the black dot had appeared. A one-way ANOVA revealed a significant difference for color selection task accuracy ($F(3,83) = 4.476$, $p = 0.006$), with Experiment 2 ($M = 49.5\%$) yielding significantly better performance than Experiments 3 ($M = 34.8\%$) and 4 ($M = 37.2\%$), but not different from Experiment 1 ($M = 38.6\%$). An ideal observer model was used to determine the attentional window size each subject deployed in response to the exogenous cue. This was then used to quantify the minimum stimulus spacing required for 75% accuracy. Minimum spacing estimates were not significantly different between Experiments ($F(3,83) = 1.732$, $p = 0.167$; Expt. 1: $M = 1.069°$, Expt. 2 $M = 0.588°$, Expt. 3 $M = 0.777°$, and Expt. 4 $M = 0.62°$) or within-subject (across the visual field). All four experiments had smaller average estimated minimum spacing for the upper and lower visual field and whole display compared to published endogenous values. Thus, regardless of stimulus size and stimulus spacing, exogenous selection operates at a finer resolution than endogenous selection at the same eccentricities.

Disclosures: C. Reynolds: None. **A.S. Greenberg:** None.

Poster

PSTR042: Mechanisms of Attention in Human

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.19/N26

Topic: H.11. Language

Support: Discovery Grant from the Natural Sciences and Engineering Research 840 Council of Canada (NSERC, RGPIN-2016-04890)

Title: Towards functional precision mapping: a systematic comparison of resting-state and task-based localization

Authors: *C. NETTEKOVEN[1], B. ARAFAT[1], D. ZHI[3], L. SHAHSHAHANI[4], A. PINHO[5], J. DIEDRICHSEN[2];
[2]Brain and Mind Inst., [1]Western Univ., London, ON, Canada; [3]Harvard Univ., Cambridge, MA; [4]Brown Univ., Providence, RI; [5]Karolinska Institutet, Stockholm, Sweden

Abstract: A major challenge in human neuroimaging is that functional regions in the brain vary highly between individuals. Numerous groups have therefore pursued a precision mapping approach, using localizing data to define functional regions at the individual level. However, which type of localizing data yields the highest precision is unclear. The cerebellum consists of a mosaic of tightly packed and highly variable functional regions, offering an ideal test case. We evaluated the ability of resting-state and task-based fMRI from 17 subjects scanned at 3T in localizing individual functional regions within the cerebellum. We compared the effectiveness of task and rest data in localizing these regions using both group maps and individual data. We also integrated the probabilistic group map with evidence from the individual data using a Bayesian model. We then used these individualized regions to predict functional boundaries in held-out data (task or rest) of the same individual. At the group level, we found that task and rest boundaries shared substantial information, but also showed some differences: While group maps derived from one modality showed much better predictive accuracy on test data from the other modality as compared to anatomical parcellations, each modality also showed some advantage in describing boundaries for the matching modality. At the individual level, we found shared individual variability between rest and task data: Boundaries based on rest data from an individual predicted the same individual's task boundaries better than those of other individuals, and vice versa. Finally, we found that integrating individual task data into a task group map increased prediction performance on held-out task data from the individual. In contrast, integrating rest data from an individual into the task group map decreased the prediction of that individual's task boundaries. These findings suggest that while task-based and resting-state fMRI data share substantial information about the individual, the functional boundaries they highlight differ considerably. We believe these findings will be useful in guiding the localization of functional regions in the brain and help inform future study designs.

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Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.01/N27

Topic: H.05. Working Memory

Support: This work was supported by the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea(NRF-2022S1A5A2A03051993)

Title: Investigating Behavioral and Prefrontal Hemodynamic Responses in Working Memory Tasks Among Individuals with Depressive Symptoms

Authors: *S. LIM[1], Y.-M. LIM[2], A.-R. KIM[2], J.-H. PARK[1];
[1]Yonsei Univ., Wonju, Korea, Republic of; [2]Yonsei Univ., Wonju-si, Korea, Republic of

Abstract: Background: While research on hemodynamic responses in the prefrontal cortex during working memory tasks has primarily focused on cognitive neuroscience, the specific stimuli contributing to working memory deficits in depressed individuals remain unclear. This study aims to investigate differences in behavioral performance and prefrontal hemodynamic responses during working memory tasks in response to various stimuli among individuals with low and high depression scores, despite lacking a clinical diagnosis.
Method: Participants were recruited through convenience sampling in South Korea and categorized based on depressive symptoms, assessed using the Center for Epidemiologic Studies Depression Scale, as high depressive (scores above 16) or low depressive (16 or below). The working memory task employed 2-back tasks within a block design. Stimuli included numbers, letters, shapes, and emotional facial expressions in randomized blocks lasting 30 seconds each. Each block included a 5-second instruction followed by 15 trials. Working memory performance was evaluated by accuracy during 2-back tasks using various stimulus types. Hemodynamic responses were measured via oxyhemoglobin (HbO) activation of the prefrontal cortex using functional near-infrared spectroscopy. Data analysis involved processing hemodynamic response data using MATLAB software and comparing high and low depressive groups using independent t-tests in SAS software.
Results: Seventy-one adults participated, with 30 classified as high depressive individuals and 41 as low depressive individuals. High depressive individuals exhibited lower accuracy during polygon and emotional facial expression-based 2-back tasks compared to controls. Abnormal HbO activation was observed in the bilateral ventrolateral prefrontal cortex under the polygon stimulus and in the left medial prefrontal cortex, bilateral orbitofrontal cortex, and bilateral ventrolateral prefrontal cortex under the emotional facial expression stimulus in high depressive individuals. However, no significant differences were found in accuracy and hemodynamic responses under number and letter conditions.
Conclusion: These findings underscore the importance of considering both visual stimuli (e.g., polygons) and affective stimuli (e.g., emotional facial expressions) in evaluating prefrontal cortex hemodynamic responses during working memory tasks in individuals with depressive symptoms. They emphasize the necessity for a comprehensive understanding of the neural mechanisms underlying depressive symptomatology, offering potential directions for future research in this field.

Disclosures: S. Lim: None. **Y. Lim:** None. **A. Kim:** None. **J. Park:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.02/N28

Topic: H.05. Working Memory

Support: ONE MUNICH Strategy Forum Next Generation Human-Centered Robotics
TUM Innovation Network Neurotechnology in Mental Health

Title: Towards the single-neuron correlates of human verbal and non-verbal working memory

Authors: *P. FAVERO[1,2], L. SCHIFFL[1,2], B. TASCI[1,2], G. ALKAN[1,2], L. M. HELD[1,2], H. CHEN[1,2], A. WAGNER[2], B. MEYER[2], J. GEMPT[3], S. N. JACOB[1,2];
[1]Translational Neurotechnology Laboratory, Dept. of Neurosurgery, Klinikum rechts der Isar, Tech. Univ. of Munich, Munich, Germany; [2]Dept. of Neurosurg., Klinikum rechts der Isar, Tech. Univ. of Munich, Munich, Germany; [3]Dept. of Neurosurg., Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

Abstract: Working memory is essential for language, which requires online maintenance and manipulation of linguistic information. It is not known whether the same neuronal mechanisms underlie the storage and processing of linguistic and non-linguistic information in working memory. Here, we present a unique case study of large-scale extracellular microelectrode recordings with single-neuron resolution from the prefrontal and parietal association cortex of an individual with stroke-induced language production impairment (non-fluent aphasia), but largely intact language comprehension and domain-general cognitive functions. We administered two delayed-match-to-sample working memory tasks comprising non-linguistic stimuli, i.e. visually presented icons drawn from eight semantic categories, and linguistic stimuli, i.e. written or spoken words matching the iconic stimuli. In the perceptual matching task (PM), the participant reported whether a test stimulus visually or auditorily matched a preceding sample. This task could be solved by comparing sensory features only. In the semantic matching task (SM), the participant reported whether the test stimulus belonged to the same semantic category as a preceding sample, thus requiring access to stimulus meaning. Our behavioral results showed ceiling performance in PM, which only mildly decreased with increasing numbers of samples (i.e. working memory load), indicating intact non-verbal working memory. Accuracy in SM was lower due to the increased task complexity, yet reached on average 87% for one sample (icons 93%, written words 88%, spoken words 81%) and 76% for two samples (icons 85%, written words 76%, spoken words 66%), suggesting largely preserved semantic knowledge, lexical access and verbal working memory. During the tasks, we acquired single-unit data from the participant's right-hemispheric middle frontal gyrus, inferior frontal gyrus, supramarginal gyrus and angular gyrus, brain hubs for working memory, semantic and conceptual processing. Ongoing analyses are exploring the degree to which different levels of symbolic reference determine the strength and fidelity of working memory coding. This study will provide deep insights into the neuronal underpinnings of human linguistic and non-linguistic cognition.

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Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

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Topic: H.05. Working Memory

Support: Czech Science Foundation, Czechia, Grant 22-28594K
National Science Centre, Poland, Grant 2021/03/Y/NZ4/00082

Title: Data-driven analysis of successful verbal memory encoding

Authors: ***P. BEGAN**[1], L. JURKOVICOVA[2], P. DANIEL[3], M. KOJAN[4], R. ROMAN[5], M. T. KUCEWICZ[6], J. CIMBALNIK[2];
[1]Biomed. engineering, [2]FNUSA ICRC, Brno, Czech Republic; [3]Brno Epilepsy Center, Dept. of Neurol. and Neurosurgery, St. Anne's Univ. Hosp. and Med. Fac. of Masaryk University, Brno, Czechia, Brno, Czech Republic; [4]Dept. of Neurol., Brno Epilepsy Center, Dept. of Neurol. and Neurosurgery, St. Anne's Univ. Hosp. and Med. Fac. of Masaryk University, Brno, Czechia, Brno, Czech Republic, Brno, Czech Republic; [5]Behavioral and Social Neurosci. Res. Group, CEITEC – Central European Inst. of Technology, Masaryk University, Brno, Czech Republic, Brno, Czech Republic; [6]Multimedia Systems, Gdansk Univ. of Technol., Gdansk, Poland

Abstract: Prediction of human memory formation remains a challenging task. Finding both the anatomical location in the brain and a reliable biomarker of neural activity could help predict successful memory encoding. In this study, we used a data-driven approach and compared a number of intracranial EEG features to reveal candidate measures and brain regions that can help establish whether a memory item has been successfully encoded.
14 epileptic patients undergoing intracranial EEG (iEEG) evaluation participated in a free-recall verbal memory task. Patients were presented with a set of 180 words and asked to recall them after a distraction phase. We calculated seven different EEG measures (power in band, Hjorth mobility, Hjorth complexity, power spectral entropy, Shannon entropy, sample entropy, multiscale entropy, and modulation index) during the encoding phase in a 100ms sliding window around word presentation (+/- 1.25 s). We used the rank-sum test to identify statistically significant differences in iEEG features between recalled and forgotten words in individual channels.
The rank-sum statistic exhibited a distinct significant (alpha=0.05) peak 100ms after stimulus onset in sample entropy (bands 4-8, 8-12 Hz) of frontal brain areas: orbital gyri and middle and superior frontal gyri. We also observed non-significant pre-onset peaks (200ms) in Hjorth mobility (20-55 Hz) and signal power (4-8 Hz) of the lingual gyrus and calcarine sulcus. These findings were consistent across different electrode contacts, task sessions, and patients.

The results of this study can help identify the proper measure, brain region, and time around item presentation that is important for the successful formation of new episodic memory traces. They can also be further utilized in machine-learning approaches to accurately predict memory encoding to guide brain-computer interface technologies for electrophysiological recording and stimulation.

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Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.04/N30

Topic: H.05. Working Memory

Support: Vilcek Scholarship

Title: High-performance decoding of verbal working memory

Authors: *J. SUN[1], S. DEVORE[2], W. K. DOYLE[3], O. DEVINSKY[4], D. FRIEDMAN[5], B. PESARAN[6];
[1]New York Univ. Vilcek Inst., New York, NY; [2]New York Univ., Brooklyn, NY; [3]NYU, New York, NY; [4]Neurol., New York Univ. Langone Hlth., New York, NY; [5]New York Univ. Langone Med. Ctr., New York, NY; [6]Neurosurg., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Successful decoding of neural activity enables brain-machine interfaces such as speech neuroprostheses and mind-powered cursor control. Despite progress decoding movement intent, decoding the cognitive processes that precede movement remains poorly understood. Verbal working memory (vWM) is a cognitive process that requires the storage and manipulation of speech. Previous studies demonstrate that vWM contents can be decoded in principle from pooled data but fail to provide individual estimates of decoding accuracy. We designed a context-dependent speech task to ask whether vWM could be decoded at the participant level. In brief, on each trial participants were presented with a rule that had to be applied to a subsequent auditory cue (one of two distinct nonsense words). The rules were "match" (repeat the token you heard) or "mismatch" (say the token you did not hear). Eight participants implanted with sEEG electrodes undergoing presurgical evaluation for drug-resistant epilepsy completed our task. We analyzed intracranial EEG activity from a total of 1,216 electrodes after bipolar re-referencing. Participants responded correctly in 78% (range: 58-92%) of trials (n=128 per patient). Incorrect responses include errors (mean: 6%, range: 0-14%) and no responses (mean: 12%, range: 4-25%). We decoded task variables on single trials by employing cluster-based nonparametric statistics in frequency, time, and space. We used leave-one-out cross-validation to avoid overfitting. We identified rule- and cue-selective electrodes in bilateral superior temporal gyrus and insula in six participants. The mean decoding accuracy (MDA) was

92.4% ($p=1.4x10^{-20}$) and 89.0% ($p=1.3x10^{-16}$) for the rule and cue, respectively. Using neural data aligned to response onset, we obtained an MDA of 89.9% ($p=1.5x10^{-17}$) in six participants for the response. Speech-selective sites were identified in the postcentral and inferior frontal gyri, as well as the anterior temporal lobe. Motor planning electrodes were identified by decoding trial outcome (no response versus correct trials) aligned to speech onset. After discarding motor planning electrodes, we observed an MDA of 79.8% ($p=2.5x10^{-12}$) for task performance before the go cue in four participants. Performance-selective electrodes were found in frontal and temporal lobes. Low frequency activity (<40 Hz) was the principal contributor to performance decoding. Our results demonstrate that cognitive processes can be decoded from intracranial EEG activity and offer the potential for targeted interventions to restore cognitive function.

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Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

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Program #/Poster #: PSTR043.05/N31

Topic: H.05. Working Memory

Support: NINDS 5K12NS129164-02

Title: Beta and high-gamma bursts predict working memory task period and performance

Authors: *V. OMELYUSIK[1], D. FAGUE[1], S. S. NAIR[1], P. D. HACKETT[2], T. DAVIS[3], E. H. SMITH[3], B. NOUDOOST[4], J. D. ROLSTON[5], B. KUNDU[1,2,3];
[1]Electrical Engin. and Computer Sci., [2]Dept. of Neurosurg., Univ. of Missouri, Columbia, MO; [3]Dept. of Neurosurg., [4]Dept. of Ophthalmology, Univ. of Utah, Salt Lake City, UT; [5]Dept. of Neurosurg., Harvard University, Brigham and Women's Hosp., Boston, MA

Abstract: Information processing in working memory (WM) may be associated with beta (12-30Hz) and high-gamma (70-140 Hz) bursts derived from local field potentials across different brain regions. Although the role of bursting has been studied in WM in non-human primates, its role in human WM is being explored. Here we show that burst characteristics are accurate predictors of WM task period (encoding vs delay vs fixation) and WM performance, in a load 3 task, in humans. We used an amplitude threshold-based criterion to extract beta and high-gamma bursts from frontal and temporal regions of interest (ROIs) from eight patients with epilepsy during an object recognition task. We characterized each trial by the average burst amplitude, burst duration, and burst number versus burst rate for beta and high-gamma frequency bands for each task period and ROI. Random forest models were used to predict task period and performance. Permutation-based feature importance analysis was used to assign importance scores to predictors.

A model trained on average burst amplitude, duration, and raw burst number within an ROI, to predict task period, attained an average test sample accuracy of 88%. The most important group of task period predictors was number of high-gamma bursts in middle temporal gyrus, middle frontal gyrus, and hippocampus. The same variables were assigned high importance scores when predicting the task period in a model considering burst amplitude, burst duration, and burst rate within an ROI (test accuracy 89%).
A model trained on average burst amplitude, duration, and burst number to predict task performance attained an average test sample accuracy of 76%. The most important predictors were amplitude of high-gamma bursts in middle temporal gyrus during fixation, encoding, and delay and the duration, amplitude, and rate of beta bursting in hippocampus. The most important predictors for a model trained on average burst amplitude, duration, and burst rate to predict task performance (test accuracy 75%) were duration and rate of high-gamma bursting in left inferior frontal gyrus during fixation.
These results provide insights into the features that may be important for predicting WM content and may be used in the future for stimulation-based treatments of WM-related dysfunction.

Disclosures: V. Omelyusik: A. Employment/Salary (full or part-time):; Kundu Lab – University of Missouri, Columbia. 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.; NINDS 5K12NS129164-02. **D. Fague:** A. Employment/Salary (full or part-time):; Kundu Lab – University of Missouri, Columbia. 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.; NINDS 5K12NS129164-02. **S.S. Nair:** None. **P.D. Hackett:** A. Employment/Salary (full or part-time):; Kundu Lab – University of Missouri, Columbia. 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.; NINDS 5K12NS129164-02. **T. Davis:** None. **E.H. Smith:** None. **B. Noudoost:** None. **J.D. Rolston:** 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.; NINDS K23 (NS114178). **B. Kundu:** A. Employment/Salary (full or part-time):; Kundu Lab – University of Missouri, Columbia. 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.; NINDS 5K12NS129164-02, NREF NSRG-P5164_20180321_170626_FE.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.06/N32

Topic: H.05. Working Memory

Support: SUNY Research Seed Grant Award 231056

Title: Trial by trial neural correlates of oculomotor control: an fmri study during visuospatial working memory task

Authors: *A. KHIBOVSKA[1], L. JIANG[2], H.-C. LEUNG[3];
[1]SUNY Stony Brook Integrative Neurosci. in Psychology, Stony Brook, NY; [2]Psychology, Stony Brook Univ., Stony Brook, NY; [3]Integrative Neurosci. Program, State Univ. of New York, Stony Brook, Stony Brook, NY

Abstract: Oculomotor control allows us to make rapid and accurate shifts in eye gaze, which is crucial for effective visual processing. Multiple cortical regions including frontal eye fields, supplementary eye fields, parietal eye fields, dorsolateral prefrontal cortex, and posterior parietal cortex are involved. However, the neural correlates in correspondence to trial-to-trial variability in saccadic eye movement control during cognitive task performance remains poorly understood. This study sought to explore whether and to what extent the saccade metrics (e.g., precision, latency, and velocity) are modulated by activity in the oculomotor control and spatial working memory network.
A group of 5 young adults (mean age = 28.2; 2F) completed both memory and visually guided saccade tasks (MGS/VGS) during functional magnetic resonance imaging. For MGS, a to-be-remembered item was displayed (0.5 sec) in different locations on the screen. Following a variable delay of 2-5 seconds, subjects recalled the item's location by a shift in eye gaze from the center fixation to the remembered location. During VGS, subjects immediately shifted their gaze to the item presented as soon as it appeared. Response precision for each trial was measured as the difference in visual angle between the target location and the saccade endpoint. Eye position was monitored and recorded using EyeLink1000 and was sampled at 1000 Hz from the right eye. Oculomotor data were screened for artifacts and noise using a custom Matlab script. High-resolution T1 MPRAGE and T2*-weighted gradient echo EPI images were acquired using a 3T Siemens Magnetom Prisma. Structural and functional images were preprocessed with HALFpipe. Preprocessed images were analyzed using two general linear models for each subject to examine how BOLD signals in correspondence to the saccadic responses are modulated by the parametric variables.
Our results replicated previous findings, showing greater activation in the medial and lateral prefrontal, posterior parietal, and visual cortices during MGS relative to VGS. In addition, we observed both positive and negative modulation of the BOLD signal in regions that are activated during visuospatial working memory responses. Notably, MGS error and latency were negatively associated with activity in different dorsolateral prefrontal and superior parietal areas, whereas such effects were much weaker during VGS. In sum, our findings suggest regions modulated by precision and latency are separable, reflecting multifaceted neural mechanisms involved in memory-guided saccadic responses.

Disclosures: A. Khibovska: None. **L. Jiang:** None. **H. Leung:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.07/N33

Topic: H.05. Working Memory

Support: SUNY Research Foundation
Burghardt Turner Fellowship

Title: 2d mixture model analysis of visuospatial working memory performance in parkinson's disease

Authors: *J. TEPAN[1,2], L. JIANG[3], M. MICHIELS[4], I. OBESO[5], H.-C. LEUNG[6];
[1]Psychology, Stony Brook Univ., New York, NY; [2]Integrative Neuroscience Progam, State University of New York, Stony Brook, Stony Brook, NY; [3]Integrative Neurosci. Progam, State Univ. of New York, Stony Brook, Stony Brook, NY; [4]Tech. Univ. of Madrid, Alcala DE Henares, Spain; [5]HM-CINAC, HM-CINAC, Madrid, Spain; [6]Integrative Neurosci. Program, State Univ. of New York, Stony Brook, Stony Brook, NY

Abstract: Visuospatial working memory (VSWM) is a crucial cognitive process that supports higher-order cognitive functions such as problem-solving, spatial navigation, and planning. Previous research has demonstrated that dopamine (DA) modulates resistance to distractors during VSWM via connections between the posterior parietal and prefrontal cortex. Prefrontal DA deficiency could severely impair memory-guided tasks that can be reversed with levodopa in rhesus monkeys. Here, Parkinson's disease (PD) is used as a model to study the effects of DA deficiency and replacement on VSWM performance. We used an EyeLink 1000 to record gaze positions in a group of PD (N=16, mean age = 63±10.9, 5F) and healthy control (HC) (N=16, mean age = 65±9.61, 10 F) participants while they performed a memory-guided saccade (MGS) and a visually guided saccade (VGS) tasks. An instruction cue was displayed at the beginning of each block of 16 MGS /VGS trials to indicate the color of the relevant dot. During the MGS task, two dots, a target and a distractor, were displayed for 0.5 sec followed by a short variable delay (1.7-4.3 sec), and a gaze shift to the target was required when the fixation cross disappeared at the end of the delay. During the VGS task, a single target is displayed followed by a response period of 2 sec wherein participants shifted their gaze immediately to the target. VSWM performance is modeled using a 2D mixture model that allows for better estimation of saccade endpoints into target-nontarget misbinding, response imprecision, and random guessing. As expected from the literature, saccade gain of both tasks was significantly reduced in the PD group compared to HC. The PD group also had significantly more variable saccade endpoints in the MGS task relative to the VGS task. However, the medication effect was only observed for latency which was significantly prolonged when the PD group was "on" compared to "off" their medication, and this effect is evident during the MGS task. It is possible that taking mediation may interrupt the intricate cognitive control within an already dysregulated system or it may reflect that the PD group adopted a different strategy to plan and execute movements with the partially remediated frontostriatal circuitry. Further, while the modeling results showed no statistical differences in the probability of guessing and swap rate between the PD and HC groups, the model supported a significantly greater variation in unsystematic error in MGS

endpoints in the PD compared to the HC group. These findings suggest that DA may not influence the guessing and misbinding components of VSWM performance, even though DA deficiency seems to impact variability in VSWM precision.

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Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

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Program #/Poster #: PSTR043.08/N34

Topic: H.05. Working Memory

Support: NIH grant DP5OD012109-01
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Title: Contingency representations in prefrontal cortex unify goal-directed planning and working memory

Authors: ***J. MILLER**[1,2], D. EHRLICH[3], E. CHO[4], N. P. SANTAMAURO[2], A. ANTICEVIC[2], J. D. MURRAY[4,2];
[1]Wu Tsai Inst., [2]Psychiatry, Yale Univ., New Haven, CT; [3]Psychology, Univ. of California, Berkeley, Berkeley, CA; [4]Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Working memory (WM) is critical in guiding our adaptive behavior based on immediate and future demands, and the prefrontal cortex (PFC) and a network of connected areas are consistently active during WM. But, it remains difficult to parse out the differential contributions of brain areas to WM function, especially when maintenance and usage of WM content is often intertwined. How do representations for stimuli, task rules, and future behavior all contribute to WM, and what is their brain circuit organization? A recently developed computational framework and task paradigm helps unify the representational geometry for goal-directed planning and WM (Ehrlich & Murray, 2022). In this conditional delayed logic (CDL) task, patterns of human behavior and activity in neural networks suggest combined representations of stimuli and task rules into response contingencies. We tested for differential neural substrates of stimulus, rule, and response information, and newly predicted contingency representations, using a version of the CDL task adapted for functional MRI.
On each trial, human participants were shown a rule cue (colored box), gabor stimulus (vertical/horizontal), followed by a jittered delay period, and then a second gabor (vertical/horizontal), after which they responded with a left or right hand button press. The correct response on each trial was determined based on a combination of the previously learned rule, and the orientation of the first and second stimuli. During the WM delay, a distributed set of voxel activity patterns in frontal and parietal cortices differentiated among contingencies across trials. Maps of contingency representations often overlapped with rule representations, however,

contingency sensitive voxels showed greater specificity to anterior PFC areas. To better understand these areal differences in task representations, we constructed neurobiologically-informed, multi-area recurrent neural networks trained on a version of the CDL task. Contingency representations emerged in higher-order areas of these networks relative to stimulus and rule representations. In sum, we show that the most anterior PFC areas in the human brain display unique representations of task contingencies and subserve WM by integrating different task information to plan future behavior.

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Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

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Program #/Poster #: PSTR043.09/N35

Topic: H.05. Working Memory

Support: NIH EY026924
NIH NS113073
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Research to Prevent Blindness

Title: Assessing changes in V4-FEF communication efficacy during working memory using optogenetic stimulation

Authors: ***P. COMEAUX**[1], L. NURMINEN[2], F. FEDERER[1], K. CLARK[1], A. ANGELUCCI[1], B. NOUDOOST[1];
[1]Univ. of Utah, Salt Lake City, UT; [2]Optometry, Univ. of Houston, Houston, TX

Abstract: Working memory (WM) is the cognitive function allowing an organism to maintain and manipulate current and relevant information in order to guide voluntary behavior. Previous work has demonstrated that WM increases the efficacy of inputs from extrastriate cortex, V4, in inducing activity in prefrontal cortex, specifically the frontal eye field (FEF). Considering the existence of coherent oscillations between visual and prefrontal areas during WM, we hypothesized that this coherence might be responsible for modulating the efficacy of communication between the areas. We used viral vectors to express channelrhodopsin-2 (ChR2) in V4 neurons and their axonal projections. By shining light within the FEF, we specifically targeted V4 neurons directly projecting to the FEF. We used a classic memory guided saccade (MGS) task wherein a rhesus macaque held a location in memory in order to plan a future eye movement for a reward. We measured the efficacy of V4 axonal terminal stimulation to drive post-synaptic activity in the FEF during different epochs of the task. We recorded from V4 and FEF sites with overlapping response fields (RFs) and compared the efficacy of communication between the areas when the content of WM matched with the overlapping RFs (IN condition)

and when WM content was in the opposite visual hemifield (OUT condition). We examined whether the local FEF oscillation and its coupling with V4 influences the efficacy of visual inputs to drive prefrontal activity. Moreover, in order to test whether manipulating V4 inputs into the FEF is sufficient to change the content of WM, we used a modified MGS task in which a distractor can compete with a WM target to be registered in memory. The goal of this experiment is to determine whether boosting V4 signals into the FEF is sufficient to guide WM-dependent behavior and whether this impact depends on coherent oscillations between the areas. By determining the influence of oscillatory coherence between areas on the efficacy of their communication and WM behavior, we aim to understand the mechanisms involved in dynamic gating of information, underlying cognitive flexibility.

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Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

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Program #/Poster #: PSTR043.10/N36

Topic: H.05. Working Memory

Support: 5 R01 NS 119519-03

Title: Mechanisms of multi-object visual working memory in macaque prefrontal cortex

Authors: *N. WATTERS[1], J. GABEL[2], M. JAZAYERI[3];
[1]MIT, Cambridge, MA; [2]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [3]Brain and Cognitive Sci., MIT Dept. of Brain and Cognitive Sci., Cambridge, MA

Abstract: Humans are adept at maintaining multiple objects in working memory. For example, as you walk around a conference poster session you can remember the locations and features of multiple posters you have recently seen. This multi-object working memory is flexible: Given a new poster session, you can easily adapt to the new set of posters. This raises a question: How does the brain encode multiple items at once in a flexible way? Several long-standing theories have attempted to answer this question. One theory is “object files,” in which there exist multiple independent neural populations, each of which may encode a single object. Another theory is “distributed resources,” in which a pool of capacity is distributed among objects and their features. A third theory is “temporal switching,” in which the brain represents only a single object at any moment but switches between objects through time. These theories have proven difficult to test behaviorally and have remained largely un-tested in the primate brain. To address this, we developed a working memory task for non-human primates (NHPs) that requires memorizing an array of visual objects. NHPs learned to perform this task and generalized to novel conditions. From two task-trained NHPs we recorded large populations of neurons simultaneously in frontal eye fields (FEF) and dorsomedial frontal cortex (DMFC), areas that

have been implicated in visual working memory.
To test hypotheses of multi-object working memory, we formulated each hypothesis as a computational constraint on neural activity. We developed encoding models that predicted moment-to-moment population activity in the brain subject to each of these constraints. These encoding models allowed us to assess how consistent each hypothesis was with the neural activity. We validated this approach using synthetic datasets satisfying each of the hypotheses. We found that neural activity in both FEF and DMFC during working memory was most consistent with a specific form of distributed resource model of working memory and was inconsistent with the object file and temporal switching models. Furthermore, the allocation of capacity inferred by the resource model predicted subsequent behavioral errors and reaction times on a trial-to-trial basis. In conclusion, our work provides neural and behavioral evidence for a particular form of resource model of visual working memory and challenges other long-standing theories. We believe this insight may also inform and constrain more detailed models of frontal cortex circuits involved in working memory.

Disclosures: **N. Watters:** None. **J. Gabel:** None. **M. Jazayeri:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.11/N37

Topic: H.05. Working Memory

Support: R01 EY017077

Title: Attractor dynamics in morph-shape working memory in macaque prefrontal cortex

Authors: *W. DANG[1], R. JAFFE[2], C. CONSTANTINIDIS[3];
[1]Vanderbilt Univ., Nashville, TN; [2]Wake Forest Univ., Winston-Salem, NC; [3]Biomed. Engin., Vanderbilt Univ., Nashville, TN

Abstract: The prefrontal cortex has been thought to represent information maintained in working memory with its neural activity commonly modelled as a ‘bump attractor’ characterized by structured recurrent excitation and feedback inhibition that allows the retention of information through a persistent neural population code. This model explains behavior and numerous features of neural activity in visual spatial tasks. However, alternative theories of working memory suggest that prefrontal cortex may serve to highlight spatial locations of stimuli or otherwise play a supervisory role rather than maintain information about remembered objects themselves. In this study, we sought to address this gap by training two macaque monkeys to execute a delayed match-to-sample task employing morphed object silhouettes, spanning five levels of similarity between the match and nonmatch (ranging from 0% to 40% morphing with 10% increments). Across 46 behavioral sessions, two monkeys exhibited performance well above chance level across the morphing axes utilized (mean performance: 90%, 86%, 78%, 63%, and 51% for 0-

40% morphing). Using multi-contact linear probes, we recorded single-neuron activity from the prefrontal cortex while the monkeys engaged in the task. Among 1659 cells recorded, 169 exhibited significant firing increases during the cue, and 218 cells displayed heightened firing during the delay period, with diverse temporal dynamics including patterns of delay-only activation, ramp-up, and ramp-down delay activity. Contrary to previous findings highlighting strong stimuli category signals, in our task, which primarily necessitates discrimination and remembering of fine shape features, PFC cells predominantly encoded distinctiveness relative to the morphing center. Furthermore, we conducted an analysis of delay-responsive cells with a sufficient number of error trials. Our findings revealed decreased persistent activity in delay period of error trials compared to correct trials following presentation of a preferred stimulus (nonparametric permutation test, $p<0.001$). Conversely, increased persistent activity was observed at the end of the delay period in error trials following presentation of a non-preferred stimulus (nonparametric permutation test, $p<0.001$). These results provide evidence that object working memory is being maintained in the prefrontal cortex and is predictive of performance in shape working memory tasks, in direct analogy of findings in spatial tasks.

Disclosures: W. Dang: None. **R. Jaffe:** None. **C. Constantinidis:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

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Topic: H.05. Working Memory

Support: STI2030-MajorProject (2021ZD0204105)
National Science Foundation of China 32271149

Title: On the transition of coding schemes for temporal orders in sequence working memory

Authors: *X. LI[1], J. CHEN[2], C. ZHANG[3], Y. XIE[4], B. MIN[1], L. WANG[5];
[1]Lin Gang Lab., Shanghai, China; [2]Ctr. for Excellence in Brain Sci. and Intelligence Technol., Chinese Acad. of Sci., Shanghai, China; [3]Institue of Neurosci., Chinese Acad. Of Scien, Shanghai City, China; [4]Lin Gang Lab., Shanghai City, China; [5]Inst. of Neurosci., Inst. of Neurosci., CAS, Shanghai, China

Abstract: How the brain processes temporal information in sequence tasks remains underexplored. Previous research found that items are stored in stable subspaces in sequence working memory, forming a static coding for temporal orders. This differs from the dynamical coding in the sensory input and response phases, where orders are directly encoded through the temporal sequence. Nonetheless, there is a lack of studies on how such a static coding scheme transforms back to dynamic coding during response. Here, we investigated the neural activity of macaque monkeys performing sequence working memory tasks and carried out analysis at both the cross-trial and single-trial levels with a specific focus on the response phase. We demonstrate

that structured rotation dynamics enables the recovery of dynamical coding of orders from the statistic coding in the memory phase. Upon go cue onset, a cascaded rotation is triggered. Precisely, with each response, one item moves out of the working memory from the rank one subspace to the response subspace, and items of subsequent orders all advance one step to the subspaces of higher rank. In this way, rotation dynamics help put items from working memory into a sequence with correct orders and enable sequential responses.

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Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

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Topic: H.05. Working Memory

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National Science Foundation of China 32271149

Title: Restricted Recurrent Neural Networks: Elucidating Circuit Mechanisms of Higher Cognition Problems through Cross-Level Modeling

Authors: *Y. ZHANG[1], X. SHEN[2], X. LI[3], G. OKAZAWA[4], L. WANG[5], J. FENG[6], B. MIN[7]; [1]Fudan Univ., Shanghai, China; [2]Peking Univ., Shanghai, China; [3]Lin Gang Lab., Shanghai, China; [4]Inst. of Neurosci., Chinese Acad. of Sci., Shanghai, China; [5]Inst. of Neurosci., Inst. of Neurosci., CAS, Shanghai, China; [6]Inst. of Sci. and Technol. for Brain-Inspired Intelligence, Fudan Univ., Coventry, United Kingdom; [7]Lingang Lab., Lingang Lab., Shanghai, China

Abstract: Given the daunting complexity of higher cognition problems, generating circuit hypotheses with mechanistic transparency is crucial, which is not achieved with “black-box” deep learning modeling approaches. Here, through introducing communication module—a rich concept recapitulating the principle of cross-level computations in biological neural systems, we developed a novel restricted RNN training framework. We demonstrated its great capability in mechanistic hypothesis generation by revealing previously unknown circuit mechanisms and confirming derived cross-level predictions in a broad range of higher cognition experiments. This framework enabled us to gain a parsimonious circuit-based geometric understanding of selection vector modulation — a core concept in flexible computation, revealing a previously unknown link between selection modulation and extra-dimensions. Also, we elucidated circuit mechanisms underlying the intriguing task-dependent representational geometry of perceptual decisions in monkey parietal cortex and provided novel predictions later being confirmed by neural data. Moreover, this modeling framework uncovered a novel circuit mechanisms for sequence working memory control. Together, the restricted RNN training framework provides a

potent avenue for uncovering novel circuit mechanisms underlying challenging higher cognition problems.

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Poster

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Topic: H.05. Working Memory

Support: Canadian Institutes of Health Research
NeuroNex
Natural Sciences and Engineering Research Council of Canada
Ontario Graduate Scholarship

Title: Neural substrates of working memory capacity limitations in the prefrontal cortex of the freely moving marmoset

Authors: *T. LO[1], S. VIJAYRAGHAVAN[1], L. E. MULLER[2], J. C. MARTINEZ-TRUJILLO[3]; [1]Dept. of Physiol. and Pharmacol., [2]Dept. of Mathematics, Western Univ., London, ON, Canada; [3]Dept. of Physiol. and Pharmacol. and Psychiatry, Schulich Sch. of Med. and Dentistry, Western Inst. for Neuroscience, Western Univ., London, ON, Canada

Abstract: Working memory (WM) is a crucial cognitive function that facilitates the retention and manipulation of information necessary for goal-oriented tasks. This capacity is inherently limited; only a finite number of items can be maintained within the WM buffers, with these constraints varying across species and sensory modalities. Previous studies in non-human primates have used fixed displays and restrained the eye position during performance of change detection tasks assessing WM capacity. They have reported that when multiple memoranda fall within the same visual hemifield, WM capacity is lower than when they are present across visual hemifields. This bilateral field effect is accompanied by a decrease in the response gain of lateral prefrontal cortex neurons when memoranda fall within the same hemifield (Buschman et al. 2011). However, this effect has not been documented in more naturalistic conditions where primates are free to move their eyes/gaze. We trained three marmosets on a delay non-match to position task using a touchscreen to investigate this issue. During the tasks, 1 to 4 stimuli were shown on the screen. In each trial presentation, the animals had to touch/select the novel stimulus, with the number of stimuli escalating from one to four as trials progressed. All animals (n=3) learned the task, showing increased performance as a function of the training session. Behavioural analysis revealed a decline in performance as the number of stimuli increased. Errors were more frequent when the novel stimulus appeared on the same side of the screen as a previously shown stimulus, consistent with the bilateral field effect. Two of these marmosets

were implanted with a multi-shank array (N-Form, Plexon Inc., TX) in the lateral prefrontal cortex areas 8/46. Neuronal responses were recorded using a wireless system (Cereplex Exilis, Blackrock Microsystems, UT). Analysis of this neuronal activity revealed distinct groups of neurons that responded significantly during three task epochs: pre-touch, post-touch, and post-reward. Additionally, we identified neurons that were tuned to stimuli located in specific quadrants on the screen and were responsive across various memory loads. We observed a significant reduction in firing rates when compared with the sum of the activities for either stimulus individually. Our results describe features of working memory capacity limitations in the common marmoset. Moreover, these results suggest that modulation in firing rates with increased memory load also occurs under naturalistic conditions, where stimulus retinotopy is not maintained by restraining eye position.

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Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

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Topic: H.05. Working Memory

Support: CIHR
Neuronex-Working Memory

Title: Diversity of spontaneous neuronal response patterns using two-photon calcium imaging and high density multielectrode arrays in murine and primate prefrontal and primary visual cortical slices.

Authors: *S. VIJAYRAGHAVAN[1], J. C. MARTINEZ-TRUJILLO[2];
[1]Western Univ., LONDON, ON, Canada; [2]Dept. of Physiol. and Pharmacol. and Psychiatry, Schulich Sch. of Med. and Dent., Western Inst. for Neurosci., Western Univ., London, ON, Canada

Abstract: Neuronal activity in mammalian cerebral cortex demonstrates a diversity of intrinsic timescales, wherein the activation of neurons show a gradient along the cortical hierarchy. Neurons in the prefrontal association cortex have the ability to generate persistent activity representing stimuli even in their absence and this has been proposed to constitute the neuronal basis of working memory. The intrinsic properties of neurons in higher-order association areas could contribute to the observation of dilated intrinsic timescales in these areas, which could in turn, contribute to the generation of persistent activity. However, the diversity in the timescales of neuronal responses across cortical areas and across species has not been systematically studied in detail. Here, we use electrical microstimulation, two-photon calcium imaging using virally delivered GCaMP6f and high density multielectrode arrays to study the intrinsic timescales of

cortical neurons in murine and primate (marmoset) brain slices from primary visual cortex and prefrontal cortex. We recorded the spontaneous cortical activity using Ca++ imaging and extracellular physiology in the presence of a modified ACSF which has been known to generate rhythmic bouts of spontaneous activity in cortical slices. We found that, both Ca++ dynamics and extracellular spiking of individual neurons showed a diversity of temporal profiles of oscillatory rhythms in prefrontal cortex and primary visual cortex. Since, with both Ca++ imaging in slices and with high density arrays are potentially capable of recording large numbers of neurons simultaneously, our methodology may be suitable to study the interareal variability and mechanisms of physiological diversity in cortical neurons.

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Poster

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.16/O2

Topic: H.05. Working Memory

Support: NSERC
DFG
NSF

Title: Regional variations in intrinsic properties of single neurons support an axis of functional specialization in primate neocortex

Authors: *M. FEYERABEND[1], S. POMMER[2], M. S. JIMENEZ-SOSA[1], J. RACHEL[2], J. K. SUNSTRUM[1], F. PREUSS[2], S. A. MESTERN[1], S. EVERLING[1], A. F. ARNSTEN[3], D. A. LEWIS[4], G. GONZALEZ-BURGOS[4], A. NEEF[5], J. F. STAIGER[2], W. INOUE[1], J. C. MARTINEZ-TRUJILLO[1];
[1]Univ. of Western Ontario, London, ON, Canada; [2]Inst. for Neuroanatomy, Univ. Med. Ctr. Göttingen, Göttingen, Germany; [3]Dept. Neurosci., Yale Med. Sch., New Haven, CT; [4]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [5]Campus Inst. for Dynamics of Biol. Networks, Univ. of Göttingen, Göttingen, Germany

Abstract: The visual system of primates is hierarchically organized. Various studies have shown that primate cortical areas show divergent properties in cytoarchitecture, neuronal densities, size, and relative proportion of neuronal types. These findings suggest that the primate neocortical expansion has been accompanied by differentiation of the intrinsic cellular machinery that support diversification of neural codes and area specialization. Here we test this hypothesis by recording intracellularly from single neurons in acute brain slices from areas V1 and the dorsolateral prefrontal cortex (dlPFC) of common marmosets (*Callithrix jacchus)*. We developed an across-species cell type classifier that uses electrophysiological intrinsic features of neurons. We trained the classifier on transgenic mouse data from the Allen Institute cell type database and

reliably identified excitatory neurons and fast spiking interneurons in sample of 374 marmoset cells. From the analyzed electrophysiological features burst spiking was significantly higher in dlPFC for both fast spiking interneurons and excitatory neurons. In addition, we identified a new type of bursting behavior in dlPFC (but not V1) fast spiking interneurons. These results demonstrate that intrinsic burst firing, a feature that enables temporal summation and plasticity in synapses during learning is prevalent in the latest stages of visual processing. The latter finding is compatible with the existence of a gradient of intrinsic properties along the visual pathways that enable different degrees of stability-plasticity across areas.

Disclosures: **M. Feyerabend:** None. **S. Pommer:** None. **M.S. Jimenez-Sosa:** None. **J. Rachel:** None. **J.K. Sunstrum:** None. **F. Preuss:** None. **S.A. Mestern:** None. **S. Everling:** None. **A.F. Arnsten:** None. **D.A. Lewis:** None. **G. Gonzalez-Burgos:** None. **A. Neef:** None. **J.F. Staiger:** None. **W. Inoue:** None. **J.C. Martinez-Trujillo:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.17/O3

Topic: H.05. Working Memory

Support: BRAIN U19 NS123714
R01 MH085974

Title: Impact of subcortical inputs on frontal cortex via MD thalamus

Authors: ***A. KAMALOVA**[1], S. TETRICK[2], M. HUANG[2], E. JANG[2], A. G. CARTER[2];
[1]New York Univ., NEW YORK, NY; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Interactions between frontal cortex and higher-order thalamus are involved in many high-level behaviors, including action selection, decision-making, and working memory. The prefrontal cortex (PFC) is driven by long-range excitatory projections from mediodorsal thalamus (MD). Communication between the PFC and MD is particularly important for cognition and disrupted in mental health disorders. However, the ability of subcortical inputs to shape activity in these thalamocortical loops is currently unknown. Here, we use viral tracing, ex vivo and in vivo electrophysiology, and optogenetics to determine how subcortical inputs engage MD to influence PFC in the mouse brain. We find that thalamocortical (TC) cells in MD receive inputs from diverse subcortical inputs, including the superior colliculus (SCm), ventral pallidum (VP), and periaqueductal grey (PAG). We show that these inputs are anatomically and functionally segregated in MD, allowing them to influence distinct subregions in the PFC. Together, our findings illustrate how subcortical inputs are routed via MD to influence activity in the PFC.

Disclosures: **A. Kamalova:** None. **S. Tetrick:** None. **M. Huang:** None. **E. Jang:** None. **A.G. Carter:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.18/O4

Topic: H.05. Working Memory

Support: R37MH085726
R01NS092096
R01MH112143

Title: Loss of Engrailed1/2 in Atoh1-derived cerebellar excitatory neurons impairs spatial working memory and alters neuronal activity in prefrontal cortex and hippocampus in mice

Authors: Y. LIU[1], M. FOX[2], B. L. CORREIA[3], A. S. LEE[4], A. L. JOYNER[5], ***D. HECK**[6]; [1]Dept. of Biomed. Sci., Univ. of Minnesota Med. Sch., Duluth, MN; [2]Anat. and Neurobio., Univ. of Tennessee Hlth. Sci. C Neurosci. Grad. Program, Memphis, TN; [3]Univ. of Pennsylvania, Philadelphia, PA; [4]Weill Cornell Med., New York, NY; [5]Developmental Biol Program, Sloan Kettering Inst., New York, NY; [6]Univ. of Minnesota Duluth, Duluth, MN

Abstract: Spatial working memory (SWM) is a cognitive skill that supports survival-relevant behaviors. In rodents, the medial prefrontal cortex (mPFC) and dorsal hippocampal CA1 region (dCA1) are jointly necessary for SWM, which can be tested by measuring spontaneous alternations during free exploration of a plus maze. Entries without repetition within 4-arm sequences are classified as correct alternations, while others are considered incorrect alternations. Previous studies in rodents have shown that SWM-based decisions about maze-arm entry are associated with increased coherence of local field potential oscillations between the mPFC and dCA1. Recent studies in mice also point to a crucial role of the cerebellum in spatial working memory and the modulation of decision related changes in mPFC and dCA1 coherence.Here, we report a SWM deficit and altered unit activity in the mPFC in mice with a loss of Engrailed1/2 expression (*En1/2*) in Atoh1-derived excitatory neurons (eCN) and granule cells (*Atoh1-En1/2* conditional knockout or KO). The cKO mice have partial loss of eCN in the medial and intermediate cerebellar nuclei, which may be partially responsible for the observe changes in unit activity and SWM deficits. SWM performance was tested in 6 KO and 6 control (CT) mice in a plus maze while simultaneously recording neuronal activity in the mPFC and dCA1 using implanted tetrodes. Electrophysiological signals were recorded with an eCube Server, and data were analyzed offline in Matlab.The number of arm visits during 12 minutes of exploration was similar between CT and KO mice. However, the percentage of correct alternations was significantly lower in KO (31.6 ± 3.4) compared to CT (39.1 ± 1.7; Two-Sample t-test, $p = 0.0394$) mice. Analysis of neuronal spike activity was time-aligned to the completion of SWM decision-making, defined as the time when all four paws entered the newly chosen maze arm. Neuronal firing rates (NFR) were compared between the KO and CT mice during the periods when mice were exploring and making decisions.In the mPFC, the NFRs (spikes/s) were higher in KO mice (14.2 ± 1.4; n = 106) compared to CT mice (10.5 ± 0.7; n =

196) (Two-Sample t-test: p = 0.0082). In the dCA1, by contrast, NFRs did not differ between KO (11.9 ± 1.7; n = 73) and CT (16.2 ± 2.0; n = 77) mice. Increased NFRs in the mPFC may be caused by altered cerebellar modulation of thalamic activity in mPFC projecting thalamic nuclei. These results are consistent with previous findings, suggesting a role of the cerebellum in SWM due to its influence on forebrain neuronal activity.

Disclosures: Y. Liu: None. **M. Fox:** None. **B.L. Correia:** None. **A.S. Lee:** None. **A.L. Joyner:** None. **D. Heck:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.19/O5

Topic: H.05. Working Memory

Support: NIH Grant NS086947
NIH Grant NS102915
NIH Grant MH119179
Walter F. Heiligenberg Professorship

Title: Neuronal firing patterns during working memory retention differ between medial prefrontal cortex layers and subregions

Authors: *J. WANG[1], Y. LI[1], W. LI[1], J. K. LEUTGEB[1,3], S. LEUTGEB[1,3,2];
[1]Neurobio. Department, Sch. of Biol. Sci., [2]Kavli Inst. for Brain and Mind, Univ. of California San Diego, La Jolla, CA; [3]Inst. for Advanced Study, Berlin, Germany

Abstract: Working memory (WM) retention relies on the coordinated activity of the medial prefrontal cortex (mPFC), hippocampus (HPC), and medial entorhinal cortex (mEC), which are all engaged in the dynamic processes of information retention and storage. These brain regions are anatomically and functionally interconnected, allowing for efficient communication and information processing during WM tasks, but with many regional and subregional differences. For instance, the ventral HPC sends direct connections to the mPFC, which vary in density between infralimbic (IL), prelimbic (PrL), and anterior cingulate (AC) cortex. Despite the observations that the connectivity differs, the precise differences in neuronal firing patterns during the retention interval between prefrontal subregions remain unclear. A better understanding of these firing patterns could provide an indication on how each subregion contributes to WM. We conducted recordings of neural activity in mPFC of rats that performed a delayed alternation task in a figure-eight maze. In particular, the task was comprised of blocks of trials in which rats were either required to run on a treadmill or allowed to rest during the delay to manipulate the persistence of theta oscillations. As expected, we observed a significantly lower theta power during resting compared to running when simultaneously recording the hippocampal local field potential. Using chronically implanted Neuropixel probes, we acquired

data from both superficial and deep layers of IL, PrL, and AC (n = 10 rats). Our analysis revealed that their deep layers exhibited higher spatial stability on the figure-eight maze compared to superficial layers. Furthermore, there was an abundance of delay-active neurons in the deep compared to the superficial layers, indicating a higher density of task-related information. Additionally, while less than 10% of neurons were identified as time cells in the superficial layers, the proportion of time cells increased to more than 20% in IL and PrL and to more than 40% in AC deep layers. We will conduct further analysis using our comprehensive neural recordings to unravel whether mPFC cell assemblies are informative about past and future trajectories. In addition, we will analyze whether the information content differs between brain states with and without ongoing theta during the delay interval. By elucidating the neuronal activity patterns across prefrontal regions and during different brain states, we will gain a better understanding of the contributions of different mPFC subregions to WM mechanisms and ultimately shed light on the neural dynamics of a broader brain system that includes HC and mEC.

Disclosures: **J. Wang:** None. **Y. Li:** None. **W. Li:** None. **J.K. Leutgeb:** None. **S. Leutgeb:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.20/O6

Topic: H.03. Decision Making

Support: HHMI
NSF DGE-2039656

Title: Neural correlates of parametric working memory in frontal and parietal cortex

Authors: *J. YANAR[1], J. KAMINSKY[1], C. D. BRODY[2,1];
[1]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]HHMI, Princeton, NJ

Abstract: Our ability to maintain and reason about continuous variables forms a core aspect of perceptual decision-making and working memory. For example, when selecting between two vendors at the market, we might encode the ripeness of the bananas at one stall into working memory in order to compare them to those of another stall further away. What are the neural codes supporting these kinds of comparisons? To investigate this, we developed a parametric working memory task in virtual reality for head-fixed mice. In the task, mice navigate down a T-maze and are shown two sinusoidal gratings of different frequencies: one at the start (Sa) and one at the end (Sb) of the stem of the T. Mice are trained to turn left at the T intersection if Sa's frequency is lower than Sb's, and right otherwise. A delay period separates the two gratings, requiring mice to maintain a representation of Sa for comparison. Previous work has suggested the medial prefrontal cortex (mPFC) and posterior parietal cortex (PPC) as potential sites of

parametric working memory maintenance. In order to test this, we are recording from both regions simultaneously during task performance using high-density silicon probes. We will examine stimulus and choice encoding in mPFC and PPC across task phases, and quantify the transfer of information between the two areas via communication subspace analysis methods. Optogenetic inactivation experiments are ongoing in both areas in order to assess their causal contribution to the task.

Disclosures: J. Yanar: None. **J. Kaminsky:** None. **C.D. Brody:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.21/O7

Topic: H.05. Working Memory

Title: Prefrontal somatostatin peptide manipulations on spatial working memory in mice

Authors: *M. HSIANG[1,2], A. BAUMAN[3], H. A. TEJEDA[4], D. A. KUPFERSCHMIDT[3], J. A. GORDON[3,5];
[1]Brown-NIH Grad. Partnership Program, Bethesda, MD; [2]National Institute of Neurological Disorders and Stroke, Bethesda, MD; [3]Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD; [4]Natl. Inst. of Mental Hlth., Bethesda, MD; [5]National Institute of Mental Health, Bethesda, MD

Abstract: Afferent pathways to the medial prefrontal cortex (mPFC) support distinct aspects of spatial working memory (SWM). Direct projections from mouse ventral hippocampus (vHPC) are crucial for the encoding of spatial cues, while projections from the mediodorsal thalamus (MD) contribute to their maintenance. However, the cellular mechanisms within the mPFC that underlie this functional specialization remain unclear. One possibility is that afferent inputs target specific subpopulations of mPFC somatostatin interneurons (SST-INs), which are thought to gate information from long-range afferents via local inhibition. Supporting this notion, inhibiting mPFC SST-INs disrupts vHPC-mPFC communication and impairs SWM performance. Therefore, the current project seeks to (1) characterize monosynaptic inputs onto mPFC SST-INs and (2) determine whether mPFC SST-IN-mediated modulation of SWM is driven by GABA or SST peptide release. To address the first aim, we used an anterograde transsynaptic tracer to map anatomical connections between vHPC or MD and mPFC SST-INs. We observed that MD targeted a greater proportion of mPFC SST-INs than vHPC, albeit in comparable layers and anterior-posterior planes. Ongoing work is assessing convergence of monosynaptic inputs from vHPC and MD onto mPFC SST-INs. To investigate a role for mPFC SST peptide in SWM, we employed two complementary approaches. First, we used a conditional knockout strategy to selectively ablate SST peptide within the mPFC. Mice lacking mPFC SST learned the SWM task at similar rates to littermate controls. Furthermore, following task acquisition, knockdown of mPFC SST did not impair SWM performance across both short (10-

second) and long (60-second) delay lengths. To further substantiate these findings, we microinfused cyclosomatostatin (c-SST), a non-selective somatostatin receptor antagonist, or vehicle into the mPFC of mice that had been trained on the SWM task. Pharmacological blockade of mPFC SST receptors did not affect SWM performance at any delay length. Collectively, these findings suggest that SST peptide signaling within the mPFC is not required for learning or performing a SWM task. Ongoing work is assessing the necessity of GABAergic transmission from mPFC SST-INs during SWM.

Disclosures: M. Hsiang: None. **A. Bauman:** None. **H.A. Tejeda:** None. **D.A. Kupferschmidt:** None. **J.A. Gordon:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.22/O8

Topic: H.05. Working Memory

Support: FY2023 MURI (ONR)

Title: Shapes of rule structures learned under different gating policies

Authors: *M. FREUND[1], D. BADRE[2];
[1]Brown Unversity, Providence, RI; [2]Brown Univ., Providence, RI

Abstract: Humans are quick and flexible learners. For example, we can learn to associate the same sensory input with different actions, dependent on contextual information held in working memory (WM). This ability is supported by hierarchical reinforcement learning, which organizes lower-order stimulus-response associations according to contexts, and it has been associated with interactions between prefrontal and striatal systems. While such learning depends on WM, the interactions between WM and hierarchical learning are underexplored. Specifically, WM can operate under different gating policies: input gating selects information to be encoded into memory, while output gating selects information to be read from memory. Notably, these gating policies are thought to depend on cortico-striatal interactions. During learning, gating policies may influence how task information is structured and retained. We explored this question by conducting a large-sample hierarchical rule learning study in humans (N=119), in which we manipulated the gating policies available to participants during learning. In each trial, participants viewed a sequence of three visual features (color, shape, texture), selected one of four responses, and received feedback. The correct stimulus-response associations were structured hierarchically, such that one feature (e.g., color) could act as a contextual cue for determining which lower-order feature signals the correct response. We manipulated gating policy by presenting the contextual cue either first (input gating) or last (output gating) in the sequence. We found that, under both learning conditions, participants reached high levels of performance and discovered the hierarchical structure at comparable rates. The learned rule

structure was also evident in a post-learning task, in which all features were presented simultaneously as a single object (no feedback). In this task, when the contextual feature switched versus repeated from one trial to the next, a switch cost was evident in slower responses and more errors. In both gating conditions, these switch costs were linked to the rate of learning, in that faster learning predicted larger hierarchical switch costs. Crucially, however, we found that the hierarchical switch costs were magnified under context-last (output gating) learning conditions. One account of this difference is that learning under an output gating policy fosters more robust hierarchical context representations. Further studies will investigate alternative explanations and will tie these effects to their underlying neural systems using cognitive and neural network models and neuroimaging.

Disclosures: **M. Freund:** None. **D. Badre:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.23/O9

Topic: H.05. Working Memory

Title: Pupil response as a non-invasive biomarker of human memory processing

Authors: ***N. HAMEDI**[1], J. GARCIA SALINAS[2], Ç. TOPÇU[1], V. S. MARKS[3], G. A. WORRELL[4], J. CIMBALNIK[5], M. T. KUCEWICZ[6];
[1]Dept. of Multimedia systems, Gdansk Univ. of Technol., Gdansk, Poland; [2]Gdansk Univ. of Technol., Gdansk, Poland; [3]Engin. Sci., Mayo Clin. Grad. Sch. of Biomed. Sci., Shalimar, FL; [4]Mayo Clin., Rochester, MN; [5]ICRC, Intl. Clin. Res. Ctr., St. Anne's Univ. Hosp., Brno, Brno, Czech Republic; [6]Multimedia Systems, Gdansk Univ. of Technol., Gdansk, Poland

Abstract: Pupil responses serve as indicators of brain processes associated with perception,attention, and decision-making. They offer an easily accessible potential biomarker forassessing human memory performance. Our goal was to assess pupil dilation as a non-invasive biomarker which differentiates between good and poor memory retrievalperformance better than invasive measures of spectral power in the intracranial EEG (iEEG)signals.Eye-tracking and iEEG signals were recorded from seven epilepsy patients (mean age of29.86 ± 16.71) performing a verbal memory task. They were presented with lists of 12 wordsfor subsequent recall, followed by a brief math distractor task. Afterwards, participants weregiven 30 seconds to recall as many words as possible in any order. Each word presentationor vocalization was treated as a single trial of encoding or recalling, respectively. Trials wereclassified as 'good' if participants recalled five or more words, and 'poor' if they recalled fouror fewer words.We estimated the average pupil size and spectral activities across various electrodes,measured within eight distinct frequency bands (delta, theta, alpha, beta, low gamma, highgamma, ripple, and fast ripple). These measurements were normalized across all patientsand sessions during the word encoding and recall trials and then were compared betweenthe two trial

types of memory performance.A two-way analysis of variance (ANOVA) was used to compare the mean pupil area betweenthe good (n = 203) and the poor trials (n = 262) drawn from all patients (N=7). We assessedthe effect of the trial type (d.f. = 1) and subject (d.f. = 6) on the normalized pupil size andaveraged spectral power-in-band.Pupils constricted during word presentation for encoding and dilated during wordvocalization for recall, consistent with our prior findings. We found that these patterns wereless pronounced during the poor performance trials. The pupils were less constricted aroundword presentation and less dilated just before word verbalization during the poorperformance trials (p-value < 0.05). These pupillometric patterns were paralleled by theinduced spectral power-in-band responses. The non-invasive pupil signal showedcomparable or greater differences between good and poor memory performance trails thanthe invasive iEEG signals.Our results show that the pupil responses provide a non-invasive measure of memoryprocessing consistent with the invasive iEEG measures. Pupil size provides a simple andaccessible alternative for memory performance biomarkers demonstrating robustmeasurement of behavioral performance and potentially also the underlying neuralactivities.

Disclosures: **N. Hamedi:** None. **J. Garcia Salinas:** None. **Ç. Topçu:** None. **V.S. Marks:** None. **G.A. Worrell:** None. **J. Cimbalnik:** None. **M.T. Kucewicz:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.24/O10

Topic: H.05. Working Memory

Support: CIHR
NSERC
Autism Research Chair Government of Ontario
CFI
NEURONEX Brain Initiative

Title: Ketamine decreases saccade related activity in lateral prefrontal cortex neurons during a virtual reality task: implications for impaired corollary discharge models of schizophrenia

Authors: *J. MARTINEZ-TRUJILLO[1], B. W. CORRIGAN[2], M. ROUSSY[3], L. PALANIYAPPAN[4];
[1]Schulich Sch. of Med. and Dentistry, Western Inst. for Neuroscience, Western Univ., London, ON, Canada; [2]Neurosci., [3]Univ. of Western Ontario, London, ON, Canada; [4]Psychiatry, McGill Univ., Dorval, QC, Canada

Abstract: Ketamine in low subanesthetic doses produces Schizophrenia (SZ) like symptoms such as working memory deficits (Roussy et al., 2021) and hallucinations (Powers et al., 2015). Some studies have proposed a disrupted corollary discharge as cause of SZ symptoms, where

signals carrying information about movements such as saccades are not properly integrated into motor plans (Thakkar et al., 2015). Dysfunction of the primate lateral prefrontal cortex (LPFC, areas 8a and 9/46) circuitry has been implicated in SZ. Here we test the hypothesis that Ketamine induced SZ like symptoms result from a disruption of the CD signal within the LPFC circuitry. We administered low doses of Ketamine to two macaque monkeys performing a working memory task in a virtual environment (Roussy et al. 2021). Eye position was unconstrained and was monitored during the task. We found that the animals' performance in the WM task was impaired by Ketamine IM administration (doses 0.2-0.7 mg/kg) relative to a saline control. Across the population of 1299 units recorded via Utah arrays, average firing rates increased. We aligned responses to saccade onset and compared perisaccadic firing rates between left- and right-ward saccades. 288 neurons responded significantly higher for saccades to the right, and 255 for saccades to the left. The mean modulation latency was ~75ms post-saccade. When we then compared saccade evoked activity pre and post ketamine injection for the preferred saccade side, we found that 75% decreased the firing rate post-Ketamine, while only 25% increase their firing rates. A subset of neurons showed decrease in firing rate during the 50ms around saccade onset and then a positive rebound response. In these neurons Ketamine decreased the amount of pre-rebound response suppression. The reported decrease in saccade selective neuronal responses and the SZ-like symptoms caused by Ketamine support the hypothesis of a disrupted corollary discharge signal within the LPFC circuitry as a possible cause of SZ symptoms.

Disclosures: J. Martinez-Trujillo: None. **B.W. Corrigan:** None. **M. Roussy:** None. **L. Palaniyappan:** None.

Poster

PSTR043: Prefrontal Circuits Underlying Working Memory

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.25/O11

Topic: H.05. Working Memory

Support: Neuronex

Title: Functional architecture of areas V1, V6 and dorsolateral prefrontal cortex cortical columns in the common marmoset

Authors: *J. PIMIENTO CAICEDO[1], J. R. DOWDALL[2], M. ABBASS[3], J. C. MARTINEZ-TRUJILLO[4];
[1]Neurosci., Robarts Res. Inst., London, ON, Canada; [2]Robarts Res. Inst., London, ON, Canada; [3]Univ. of Western Ontario, London, ON, Canada; [4]Dept. of Physiol. and Pharmacol. and Psychiatry, Schulich Sch. of Med. and Dent., Western Inst. for Neurosci., Western Univ., London, ON, Canada

Abstract: The primate visual system is hierarchically organized with thalamic inputs reaching area V1 and propagating through different areas until reaching the lateral prefrontal cortex

(LPFC) (Felleman & Essen, 1991). A tacit assumption has been that each cortical area contains microcircuits composed of canonical motifs, and that differences in function across areas are due to their distinctive intra- and inter area connectivity. However, an alternative view is that cortical microcircuits vary in their structural and functional properties across the hierarchy of visual processing, and one will find variations of the canonical circuit motif that impact the function of individual neurons and population dynamics. To test this hypothesis, we used simultaneous neuropixel recordings orthogonal to the cortical surface in areas V1, V6 and LPFC (Area 8a/46) of two common marmosets (Callithrix jacchus) in two different conditions. First, when animals were positioned in front of a gray screen (resting state), and second, passive viewing of static images and clips of animated cartoons (length: 5 to 20 s). We spike sorted the data and isolated single neurons along different cortical layers. We observed that V1 and V6 had higher firing rates and higher spike train variability than LPFC cells ($p < 0.05$, Dunn's test with Bonferroni correction). We found at least three clear types of response profiles in single neurons: bursting, regular spiking, and oscillatory. Bursting cells tended to fire in clusters of spikes with Inter Spike intervals (ISIs) < 10 ms. Regular spiking cells fired in a Poisson-like manner, and oscillatory cells (almost exclusively found in V1) fire repetitively in time-locked windows. We found that the number of bursting cells decreased as a function of anteroposterior position, with more bursting cells in V1. In contrast, regular spiking cells were more abundant in frontal areas. These results suggest that the functional architecture of the visual system varies across brain regions supporting the view of variations in canonical circuit motifs that impact the different areas' functional role in visual processing.

Disclosures: J. Pimiento Caicedo: None. **J.R. Dowdall:** None. **M. Abbass:** None. **J.C. Martinez-Trujillo:** None.

Poster

PSTR044: Social Cognition: Animal Behavior

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.01/O12

Topic: H.06. Social Cognition

Support: Inflammation Healing Foundation-HP
1R01MH131592-01A1 -ML
1P20GM144041-01A1 -BG

Title: Early life sleep disruption alters densities of perineuronal nets and oxytocin neurons in the paraventricular nucleus of adult prairie voles

Authors: *J. J. BABU[1], J. L. SMITH[2], C. J. TINSLEY[3], N. E. MILMAN[4], L. REXRODE[2], J. HARTLEY[2], B. GISABELLA[1], M. M. LIM[5], H. PANTAZOPOULOS[1];
[1]Psychiatry, Univ. of Mississippi Med. Ctr., Jackson, MS; [2]Med., Univ. of Mississippi Med. Ctr., Jackson, MS; [3]Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR; [4]Behavioral

Systems Neurosci., OHSU, Portland, OR; [5]Behavioral Neurosci., VA Portland Hlth. Care Syst., Portland, OR

Abstract: Background: Autism Spectrum Disorders (ASD) affects 1 in 59 children and is four times more likely in males. Diagnosis typically occurs before age 3, the critical period for early brain development. Children spend more time in REM sleep, which is important in shaping neuronal circuitry. Several studies suggest that children with early-life sleep disruption (ELSD) are more likely to develop ASD. However, little is known about how ELSD contributes to neuropathological changes in ASD. Previous animal studies from our group demonstrated that ELSD resulted in impaired social behaviors in adult prairie voles, including reduced partner preference in this typically monogamous species. Our recent study identified alterations of extracellular matrix molecules (ECMs) in the brains of children with ASD. ECM molecules are critically involved in neurodevelopment. Perineuronal nets (PNNs) are ECM structures composed of chondroitin sulphate proteoglycans (CSPGs) involved in neuronal maturation and synaptic plasticity implicated in neurodevelopmental disorders. PNNs are present in the paraventricular nucleus (PVN), a region that synthesizes oxytocin, a neurotransmitter involved in promoting social behaviors. We tested the hypothesis that ELSD results in alterations in PNNs in the PVN of adult voles and is associated with altered numbers of oxytocin neurons. **Methods:** Histochemistry for wisteria floribunda agglutinin (WFA) and immunofluorescence for WFA, oxytocin, and nestin was conducted on fixed free floating serial sections containing the PVN from male and female adult voles with ELSD (n=8) and controls (n=6). Stereology-based microscopy was used to quantify numerical densities of PNNs and co-localization of PNNs and WFA+ neurons with oxytocin neurons and nestin cells as a marker for immature neurons. **Results:** Densities of WFA+ PNNs and intracellular WFA-labeled neurons were increased in male voles with ELSD ($p<0.05$). Male voles with ELSD displayed decreased densities of oxytocin+ neurons ($p<0.04$) and increased densities of oxytocin+ neurons co-labeled with nestin ($p<0.04$). **Conclusion:** Our data suggest that ELSD contributes to altered PVN neurodevelopment. Increased PNN densities indicate restricted PVN synaptic plasticity. Furthermore, decreased oxytocin neurons and increased co-expression with nestin indicate impaired oxytocin neuron maturation in ELSD voles. Our findings provide evidence for how ELSD may contribute to male-specific alterations in social behavior, including reduced partner preference behavior**.** Ongoing studies will examine the impact of ELSD on additional molecules implicated in our human postmortem ASD studies.

Disclosures: J.J. Babu: None. **J.L. Smith:** None. **C.J. Tinsley:** None. **N.E. Milman:** None. **L. Rexrode:** None. **J. Hartley:** None. **B. Gisabella:** None. **M.M. Lim:** None. **H. Pantazopoulos:** None.

Poster

PSTR044: Social Cognition: Animal Behavior

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.02/O13

Topic: H.06. Social Cognition

Support: NIH R01MH131592
Portland VA Research Foundation

Title: Supervised annotation of affiliative and aggressive behaviors in adult prairie voles exposed to early-life sleep disruption

Authors: *L. S. BUENO-JUNIOR[1], N. E. P. MILMAN[2], A. GHIMIRE[1], C. E. J. TINSLEY[2], P. T. WICKHAM[2], Y. HU[3], B. YE[3], M. M. LIM[2], B. O. WATSON[1];
[1]Dept. of Psychiatry, Univ. of Michigan Med. Sch., Ann Arbor, MI; [2]Oregon Hlth. and Sci. Univ. and Veterans Affairs Portland Hlth. Care Syst., Portland, OR; [3]Life Sci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Prairie voles (Microtus ochrogaster) are uniquely suited for investigating dyadic male-female interactions due to their species-typical tendency to form monogamous bonds. Reproducible methods to manipulate these behaviors are essential for the systematic study of social alterations and their physiological correlates. One such method - termed early-life sleep disruption (ELSD) - was developed by our group and involves selective disruption of REM sleep in prairie voles during postnatal days 14-21 (Jones et al., 2019 - Sci Adv). Through manual behavioral scoring, we demonstrated in that work that adult prairie voles exposed to ELSD are less affiliative with opposite-sex conspecifics and have impaired pair bond expression. Subsequently, in another study, we employed supervised keypoint tracking (DeepLabCut) to analyze long-term (72-h) home-cage recordings of wire-mesh separated male and female voles, revealing more nuanced behavioral changes in ELSD subjects, including a decrease in male body orientation toward the female and a disruption of ultradian rhythms in female locomotor activity (Bueno-Junior et al., 2023 - R Soc Open Sci). While these findings revealed temporal and spatial details of ELSD impacts, they did not capture the complexity of unrestricted dyadic interactions. In the present study, we use supervised behavioral annotation (LabGym) to analyze freely interacting male-female pairs. Our findings demonstrate that ELSD reduces the incidence of anogenital sniffing in males and increases the vigor of aggressive reactions in females, reinforcing the sex-specificity of ELSD effects. Moreover, we observe distinct temporal dynamics in two mutually-exclusive resting behaviors - huddling and solitary idling - which are currently being examined for ELSD impacts. These observations and automated system will fuel future research integrating behavior and physiology and may enhance our understanding of the long-term social alterations stemming from poor sleep during early development, including in conditions such as autism spectrum disorders.

Disclosures: L.S. Bueno-Junior: None. **N.E.P. Milman:** None. **A. Ghimire:** None. **C.E.J. Tinsley:** None. **P.T. Wickham:** None. **Y. Hu:** None. **B. Ye:** None. **M.M. Lim:** None. **B.O. Watson:** None.

Poster

PSTR044: Social Cognition: Animal Behavior

Location: MCP Hall A

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Program #/Poster #: PSTR044.03/O14

Topic: H.06. Social Cognition

Support: NIH R01 Award MH131592
NIH T32 AA007468-36

Title: Sex-specific impacts of early life sleep disruption: ethanol seeking, social interaction, and anxiety are differentially altered in adolescent prairie voles

Authors: *D. E. GINDER[1], C. J. TINSLEY[2], M. E. KAISER[3], M. M. LIM[3];
[1]Oregon Hlth. and Sci. Univ., Portland, OR; [2]Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR; [3]VA Portland Hlth. Care Syst., Portland, OR

Abstract: Early life sleep is important for shaping brain and behavior later in life. Using an early life sleep disruption (ELSD) paradigm in the highly-social prairie vole, we have previously reported that ELSD from Postnatal Day 14 (P14) to P21 (pre-weaning) caused long-lasting deficits in social bonding and stress reactivity later in adulthood. However, we have not previously examined the effects of ELSD on adolescence, which is a critical developmental timepoint for shaping behavior into adulthood. To fill this gap, we examined social interactions, anxiety-like behavior (as measured by a light/dark box), and reward related behaviors (measured via two-bottle choice with ethanol and social interactions) after ELSD at the adolescent time point. In the social interaction test, adolescent voles of both sexes that underwent ELSD interacted with their sibling significantly less, compared to controls. Interestingly, male voles showed reduced number of self-grooming events compared to females, but no differences in autogrooming were found between adolescent male ELSD and control voles. In the light-dark box, adolescent animals that underwent ELSD showed reduced rearing activity in both the light and dark side of a light/dark box compared to controls. Adolescent ELSD female prairie voles also showed less activity in the light compared to controls, and adolescent female ELSD voles showed less overall activity compared to male ELSD voles. In the two-bottle choice paradigm, both male and female ELSD adolescent voles showed reduced ethanol preference and ethanol consumption. Taken together, these results suggest ELSD results in increased anxiety-like behavior in female prairie voles and reduced reward seeking behavior in both male and female prairie voles at the adolescent time point following ELSD. These results further suggest that early life sleep is critically important for the proper development of neurotypical behaviors in adolescence. This work was supported by NIH R01 Award MH131592 to MML and NIH T32 AA007468-36 to DEG. These contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

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Poster

PSTR044: Social Cognition: Animal Behavior

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.04/O15

Topic: H.06. Social Cognition

Support: 1R01MH131592

Title: Early-life sleep disruption drives precocious development of perineuronal nets while in vivo ChondroitinaseABC treatment reverts molecular and behavioral trajectories back to adolescence in adult prairie voles

Authors: *N. MILMAN[1,2], J. LOEUNG[1], N. MCGUIRE[1], C. J. TINSLEY[3], L. S. BUENO-JUNIOR[4], J. BABU[5], H. PANTAZOPOULOS[6], B. O. WATSON[4], B. A. SORG[7], M. M. LIM[8]; [1]OHSU, Portland, OR; [2]Behavioral Neuroscience, Oregon Health and Science University, Portland, OR; [3]Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR; [4]Dept. of Psychiatry, Univ. of Michigan, Ann Arbor, MI; [5]Univ. of Mississippi Med. Ctr., Jackson, MS; [6]Neurobio. and Anatom. Sci., Univ. of Mississippi Med. Ctr., Jackson, MS; [7]Neurobio., Legacy Res. Inst., Portland, OR; [8]VA Portland Hlth. Care Syst., Portland, OR

Abstract: Intro: Early life sleep is essential for species-typical neurodevelopment, including the formation of functional networks and display of affiliative social behavior. Proper mapping of Parvalbumin (PV+) interneurons and the appearance of the surrounding extracellular matrix structure (Perineuronal Nets - PNNs) together are widely assumed as evidence of cortical maturation. Prairie voles (*Microtus ochrogaster*) are highly affiliative, maximally so during adolescence, and as adults, exhibit monogamous pair bonding. We found that experimentally reduced rapid-eye-movement (REM) sleep during the 3rd post-natal week (P14-21, herein ELSD) reduces partner preference behavior between opposite-sex pairs of adults, and also increases PV+ cells. However, it is unclear how ELSD alters the formation of PNNs during adolescence within later-maturing cortical structures relevant to affiliation. Methods: At P21 (weaning) or P28, brain tissue was harvested from male and female voles after exposure to ELSD or control conditions. Immunohistochemistry and fluorescent microscopy identified PV+ cells at the two adolescent time points, and analyzed images using an automated software (Imaris). In a separate cohort of adult prairie voles (P80), we injected ChondoitinaseABC (ChABC, an enzyme to remove PNNs *in vivo*) or Sham injections in the somatosensory cortex. Same-sex sibling cagemates were placed in a novel-home cage to explore and interact at the following time points: P28 (Cohort 1) or 48hrs post-surgery (Cohort 2) and behavior was manually scored for huddling, allogrooming, nose-to-nose contact and play behavior. Results: Mean intensity of PNNs significantly increased from P21 to P28. Furthermore, PV mean intensity increased in only those cells surrounded by PNNs. ELSD caused a rightward shift starting at P21 and persisting until P28 in mean intensity of PNNs surrounding PV+ cells, specifically in Layer 4 of the somatosensory cortex. Injection of ChABC *in vivo* reduced the intensity and number of PNNs proximal to the injection site. In adults, ChABC increased affiliative behavior compared to sham injected animals (Cohort 2), approaching high levels typically seen during adolescence (Cohort 1). Discussion: Our data suggest that ELSD accelerated maturation of PV+ interneurons in cortical structures. Removal of PNNs using ChABC in adult voles appeared to revert the mature cortex to an adolescent state and, consistent with this notion, increased adolescent-like affiliation in these adults. This work supports further research into how early life sleep may shape typical social development via modulation of later-maturing cortical circuits involved in affiliation.

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Poster

PSTR044: Social Cognition: Animal Behavior

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.05/O16

Topic: H.06. Social Cognition

Support: VA Merit 01BX006155

Title: Characterization of acute and chronic behavioral impairments after combined TBI and PTSD in mice

Authors: *P. WICKHAM[1,2], K. L. MCDANIEL[1,2], Z. POTTER[1,2], L. NUNGARAY[1,2], C. E. TINSLEY[1,2], M. M. LIM[3,4];
[1]Oregon Hlth. and Sci. Univ., Portland, OR; [2]Veterans Affairs Portland Health Care System, Portland, OR; [3]VA Portland Hlth. Care Syst., Portland, OR; [4]Oregon Health and Science University, Portland, OR

Abstract: Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are both independently associated with an increased risk of developing neurodegenerative diseases such as Parkinson's disease, and recent evidence suggests that the combination of TBI+PTSD synergizes this risk. However, few studies have systematically examined the time course of behavioral impairment in mice with the comorbid TBI+PTSD condition. Identifying the timing of the onset of behavioral impairments in response to TBI+PTSD is important, in order to inform the optimal timing of potential interventions to prevent the progression of neurodegenerative diseases. To fill this gap, we examined the time course of behavioral impairments following neurotrauma (TBI+PTSD) in mice. We assigned 3-month-old male and female mice to an experimental or control group. Experimental mice underwent single prolonged stress (SPS) followed by controlled cortical impact (CCI) to induce PTSD and TBI, respectively, in a combined TBI+PTSD model. We then quantified gait, cognition, and anxiety-like behaviors at 2 weeks, 1 month, and 3 months post-TBI+PTSD, compared to controls and found that behavioral impairments persist long-term. The results from these experiments illustrate the timing of behavioral mechanisms associated with TBI, PTSD, and the progression of neurodegenerative diseases.

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Poster

PSTR044: Social Cognition: Animal Behavior

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Program #/Poster #: PSTR044.06/O17

Topic: H.06. Social Cognition

Support: VA Merit Award 01BX006155
NCCIH U19 AT010829

Title: Non-invasive sleep staging using electric field sensors in mice: Relevance to neurotrauma, REM sleep behavior disorder, and neurodegeneration

Authors: *C. E. TINSLEY[1], K. MCDANIEL[2], P. WICKHAM[3], N. E. GRAY[1], H. KLOEFKORN[4], M. M. LIM[2];
[1]Oregon Hlth. and Sci. Univ., Portland, OR; [2]VA Portland Hlth. Care Syst., Portland, OR; [3]OHSU, Portland, OR; [4]Chemical, Biol., and Envrn. Engin., Oregon State Univ., Corvallis, OR

Abstract: Sleep disorders such as Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD), insomnia, and hypersomnia are commonly associated with neurodegenerative diseases. The gold standard for measuring sleep in animal models is surgically implanted electroencephalogram (EEG) and electromyogram (EMG) electrodes for staging of vigilance states. However, this method has significant limitations due to risks associated with this invasive surgical procedure and recovery. In aged mice and/or mice exposed to neurotrauma, these risks are even greater and thus, non-invasive sleep staging methods are needed. However, prior attempts at non-invasive sleep assessments were largely unable to accurately resolve REM from non-REM (NREM) stages, which is critical in order to accurately model traumatic brain injury (TBI), posttraumatic stress disorder (PTSD), neurotrauma (TBI+PTSD), and REM sleep behavior disorder (RBD) in rodents. In order to address this gap, we applied electric field (EF) sensors, affixed externally to the home cage, as a highly sensitive measure of respiration and gross-body movements. The combination of EF-derived signals was validated against gold standard intracranial EEG/EMG recordings. Our results showed that EF sensors accurately staged REM, NREM, and wake at comparable rates to traditional EEG/EMG-based methods in aged male mice. In summary, EF sensor technology has high potential to eliminate several limitations associated with the current, more invasive, methods of recording sleep and is a promising method to assess sleep in mouse models of neurotrauma, RBD, and neurodegeneration.

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Poster

PSTR044: Social Cognition: Animal Behavior

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Program #/Poster #: PSTR044.07/O18

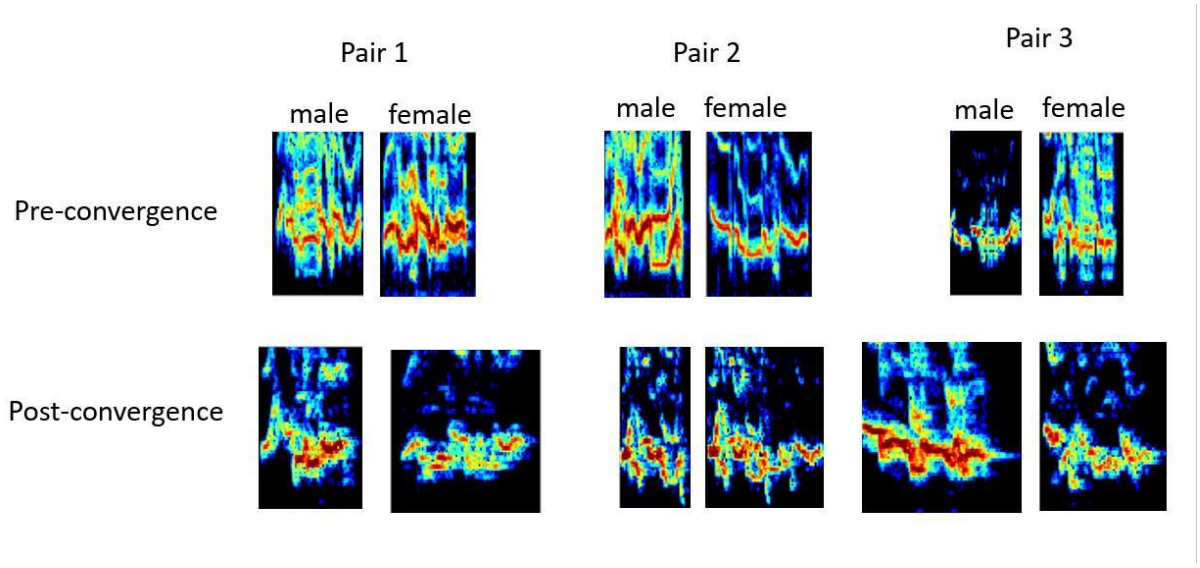
Topic: H.06. Social Cognition

Support: Ann S. and Robert R. Morley Student Research Fund
CALS Charitable Trust Research Support Program

Title: Examining the effect of audience on budgerigar social communication

Authors: *F. S. NEMON[1], Z. ZHAO[2], J. H. GOLDBERG[1];
[1]Neurobio. and Behavior, Cornell Univ., Ithaca, NY; [2]Cornell Univ. Neurobio. and Behavior, Ithaca, NY

Abstract: Humans communicate differently with distinct individuals, a phenomenon known as the audience effect. Budgerigars, a highly social parakeet, imitate one another's vocalizations even as they maintain sufficient subtle acoustic differences to preserve individuality. Here we examine for a possible audience effect by testing if distinct known social partners elicit individually-targeted vocalizations. We established three bonded pairs (each pair consisting of one female and one male) of unfamiliar birds with different contact calls. The pairs were placed in a behavioral arena equipped with directional microphones and cameras to record call convergence and courtship behavior. As expected from past work (Brockway, 1964; Farabaugh et al, 1994; Striedter et al, 2003), initial pairs (pairing A) converged their calls, and in this experiment, to different degrees over the course of ten weeks. The males will now switch females to observe changes in courtship behavior and vocalizations with different females (pairing B). Once the males converge their calls in the second pairing, they will return back to pairing A to determine if males remember their previously converged contact calls. Gestures, contact calls, and warble calls will be evaluated for each male using machine learning techniques recently developed in the Goldberg lab. At stake in these experiments is if budgerigars instantly change what they 'say' to different individuals - such a result would highlight the increased cognitive capacity for these animals than previously known. More broadly, these initial behavioral studies will set the stage for future neuroscientific studies to test which neural circuits and signals enable an animal to transform a social recognition signal into a vocal motor output.



Disclosures: **F.S. Nemon:** None. **Z. Zhao:** None. **J.H. Goldberg:** None.

Poster

PSTR044: Social Cognition: Animal Behavior

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.08/O19

Topic: H.06. Social Cognition

Support: 2R01MH104602

Title: Social cognition deficits in the J20 mouse model of Alzheimer's disease

Authors: *R. MORAIS-RIBEIRO[1,2], D. PIMPINELLA[1], T. BOCK[1], T. G. OLIVEIRA[2], S. A. SIEGELBAUM[1];
[1]Columbia Univ., New York, NY; [2]ICVS / Sch. of Medicine, Univ. of Minho, Braga, Portugal

Abstract: The hippocampal CA2 subregion plays important roles in regulating social behavior. It is required for the encoding, consolidation, and recall of social novelty recognition memory, which is essential to discriminate a novel from a familiar conspecific, and acts to promote social aggression. CA2 dysfunction has been implicated in a number of neurological and psychiatric disorders associated with abnormal social behavior, including epilepsy, schizophrenia, and different forms of dementia. Recent studies of the Tg2576 mouse genetic model of Alzheimer's disease (AD) reported a decrease in inhibitory synaptic transmission and synaptic plasticity that contributes to social memory deficits. Here we explore a second genetic model of AD, the J20 mouse line, to determine whether social memory deficits and altered CA2 function are a common feature of AD mouse models. In our preliminary results, we found that male and female J20 mice show increased mobility in an open field test, in line with previously reported hyperactivity phenotype observed in these mice. Moreover, male and female J20 mice show relatively normal levels of sociability, the preference to explore a novel mouse inside a wire cup cage compared to an empty cup. We then subjected the mice to a CA2-dependent social novelty recognition task, in which a subject mouse explores an open arena containing a novel conspecific and a previously encountered conspecific confined to separate wire cup cages. Social memory is manifested by the preference of the subject to explore the novel mouse. Male J20 mice showed a significant impairment in this task. Strikingly, age-matched female J20 mice showed a normal social memory behavior. In preliminary electrophysiological experiments in ex vivo hippocampal slices, we have so far failed to observe a significant difference in either intrinsic electrophysiological properties of CA2 pyramidal neurons or in the amplitude of excitatory or inhibitory synaptic potentials evoked by electrical stimulation of the hippocampal or cortical inputs to CA2 in J20 compared to wild-type mice. Future experiments will explore whether the deficit in social memory is associated with altered in vivo activity of CA2 neurons in this AD mouse model.

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Poster

PSTR044: Social Cognition: Animal Behavior

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.09/O20

Topic: H.06. Social Cognition

Title: Differential effects of Thrombospondin-1 deletion on cognition and tau pathology in the KKAy mouse model of metabolic syndrome

Authors: *F. ALMASHHORI[1,2,3], A. MATHIAS[4], J. TREADWAY[4], P. RAMAN[4,3], S. M. FLEMING[1,3];
[1]Dept. of Pharmaceut. Sci., Northeast Ohio Med. Univ., Rootstown, OH; [2]Department of Integrative Medical Sciences, Northeast Ohio Medical University, Rootstown, OH; [3]Biomedical Science Graduate Program, Kent State University, Kent, OH; [4]Dept. of Integrative Med. Sci., Northeast Ohio Med. Univ., Rootstown, OH

Abstract: Metabolic syndrome (MetS) amplifies the risk of dementia. Earlier work from our lab and others have shown hyperphosphorylated tau, a hallmark pathology of Alzheimer's disease (AD), in mouse models of MetS. Thrombospondin-1 (TSP1), an astrocyte-secreted protein, regulates synaptogenesis and neurogenesis in the developing brain. Previous studies report reduced TSP1 expression in the brains of AD patients and mouse models. While we and others have reported that hyperglycemia, characteristic of MetS, upregulates TSP1 expression in the plasma and multiple tissues, the role of TSP1 in regulation of MetS-induced cognitive dysfunction is unclear. The goal of the present study was to investigate the effect of global TSP1 loss-of-function (LOF) in a mouse model of MetS (KKAy), with a focus on cognitive function and brain tau pathology. Male and female non-agouti $KKAy^{-/-}$ (non-MetS) and agouti $KKAy^{+/-}$ (MetS) mice, with and without TSP1, were fed a standard diet and aged to six months. Body weight, blood glucose, total cholesterol and triglyceride levels were measured to confirm MetS. Cognitive function was measured using a battery of tests including the Barnes maze test of spatial memory, Y-maze test of working memory, and an object recognition test. Total and phosphorylated tau (ptau: S202, T231) expression was measured in frontal cortex and hippocampal tissue using western blotting. Behaviorally, male $KKAy^{-/-}$ with $TSP1^{LOF}$ showed increased investigation time in object recognition test and were faster to reach the target opening in Barnes test during the probe trial compared to both $KKAy^{-/-}$ with intact TSP1 and $KKAy^{+/-}$ with $TSP1^{LOF}$. Consistently, male $KKAy^{-/-}$ with $TSP1^{LOF}$ showed reduced hippocampal and frontal cortex ptau (S202, T231) vs. $KKAy^{+/-}$ with $TSP1^{LOF}$ plus a trend for reduced ptauS202 in the hippocampus vs. $KKAy^{-/-}$ with intact TSP1. Although hippocampal ptauS202 was reduced in male $KKAy^{+/-}$ with $TSP1^{LOF}$, no difference in cognitive function was noted between $KKAy^{+/-}$ with and without TSP1. In female mice regardless of $TSP1^{LOF}$, $KKAy^{-/-}$ showed an increase in investigation time in the object recognition test vs. $KKAy^{+/-}$ mice. $TSP1^{LOF}$ increased

hippocampal ptauT231 in both female genotypes. Further, only female KKAy$^{-/-}$ with TSP1^{LOF} were faster to reach the target opening in the Barnes test during the probe trial. These results indicate a potential beneficial effect of TSP1 loss in male non-agouti KKAy$^{-/-}$ versus detrimental effects in female agouti KKAy$^{+/-}$. Of note, beneficial effects of TSP1 loss in male non-agouti mice were lost in the setting of MetS. Overall, our data suggest sex-specific differential effects of TSP1^{LOF} on cognitive function and tau pathology in MetS.

Disclosures: F. Almashhori: None. **A. Mathias:** None. **J. Treadway:** None. **P. Raman:** None. **S.M. Fleming:** None.

Poster

PSTR044: Social Cognition: Animal Behavior

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.10/O21

Topic: H.06. Social Cognition

Support: NIMH Grant R01MH127423

Title: Dissecting the role of epigenetic reader PHF21B in social interaction

Authors: *J. HE, Y. HUANG, Q. MA, H. RUAN, J. LICINIO, M.-L. WONG;
Psychiatry and Behavioral Sci., State Univ. of New York Upstate Med. Univ., Syracuse, NY

Abstract: Social cognitive impairments are a significant concern and a central feature of several neurodegenerative and neuropsychiatric disorders. The plant homeodomain finger protein 21B (PHF21B) is a member of the histone demethylases superfamily that functions as an epigenetic reader whose dysfunction is implicated in major depressive disorder. Our previous data show that PHF21B is an epigenetic reader for H3K36m3. Alterations in genes encoding for methyltransferases specific for H3K36me3 can cause defects in social interaction. However, the effect of PHF21B on social interaction remains unclear. The objective of this study is to investigate the role of PHF21B in social interaction. We generated a PHD finger protein 21B-depleted (Phf21b depleted) mutant CRISPR mouse model (hereafter called Phf21bΔ4/Δ4) to examine Phf21b's role in social interaction. Three-chamber tests and five-trial tests were used to evaluate social memory. The olfactory habituation/dishabituation test was performed to investigate olfactory function. Immunofluorescence was performed to detect AMPAR subunit glutamate receptor GLUR1-expressing synapses and PSD95-positive synapses in the hippocampus, as well as oxytocin in different brain regions. Glutamatergic synaptic transmission in the hippocampus was evaluated ex vivo by electrophysiology. We found that Phf21bΔ4/Δ4 mice exhibited impaired social memory and increased aggression but showed no effect on olfactory ability. A reduction in synaptic protein expression and impaired long-term potentiation was observed in Phf21bΔ4/Δ4 hippocampi. Furthermore, PHF21B modulated oxytocin which is associated with social behaviors. Phf21bΔ4/Δ4 mice have reduced the level of oxytocin in the forebrain, third ventricle, pituitary, and cerebral cortex. In conclusion, these results establish

PHF21B as an important upstream regulator of social behavior-related genes and a potential therapeutic target for neurobehavioral disorders in mice.

Disclosures: **J. He:** None. **Y. Huang:** None. **Q. Ma:** None. **H. Ruan:** None. **J. Licinio:** None. **M. Wong:** None.

Poster

PSTR044: Social Cognition: Animal Behavior

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.11/O22

Topic: H.06. Social Cognition

Support: SFARI ARC

Title: Social cooperative learning deficits in a rat model of Fragile X Syndrome

Authors: *A. SHUKLA[1], E. RIVERA MELENDEZ[2], S. P. JADHAV[3];
[1]Brandeis Univ., Waltham, MA; [2]Brandeis Univ. Grad. Neurosci. Program, Waltham, MA; [3]Psychology, Brandeis Univ., Waltham, MA

Abstract: Cooperation is a complex prosocial behavior that entails voluntary collaborative actions aimed at mutual benefit. This requires simultaneous monitoring of self-actions and those of others, thus being socially as well as cognitively taxing for the animals. In natural conditions, social cooperation has been reported to manifest across a range of species in their day-to-day interactions and decision-making processes in pursuit of common objectives (Krebs & Davis, 1993; Kappeler & van Schaik 2006). Further, several neuropsychiatric disorders such as autism spectrum disorders (ASDs), major depressive disorders (MDDs), etc. are associated with severe social and cognitive impairments, and studying cooperative behavior in the context of these disease models is necessary for our understanding of complex interplay between social cognition and communication in typical and diseased individuals. To address this gap, we developed a novel behavioral paradigm in spatial W-mazes aimed at investigating social cooperative learning in wild type rats and a rat model of fragile X syndrome (FXS), the leading monogenetic cause of ASDs and intellectual disability. Rats were required to coordinate with their peers in space and time by visiting matching arms on paired W-mazes to seek mutual rewards on a probabilistic schedule. Preliminary results show that wildtype (WT) male rats (N = 8), running as dyads, successfully learned to coordinate with each other and perform successful cooperative transitions to matched wells in the mazes. In contrast to WT littermates, *Fmr1-/y* rats (N = 8, Long Evans background) were impaired in making cooperative transitions to their peer-occupied arms in the maze. Masking of visual cues from the peer resulted in performance deterioration in both WT and *Fmr1-/y* rats, thus demonstrating a critical role of these cues in mediating successful cooperative transitions in these rats. Quantification of peer-directed head orientations indicated that both WT and *Fmr1-/y* rats show comparable rates of peer-directed head orientations in successful trials as followers. Further, a closer look at the choice sequences of the rats revealed

that while the WT rats converge upon an optimal sequence of choices with training, *Fmr1-/y* rats fail to do so. Taken together, these findings clearly point towards deficits in social cooperative learning in *Fmr1-/y* rats relative to their WT counterparts, and demand a critical examination of neural circuit mechanisms mediating this behavior in WT rats and corresponding deficits in *Fmr1-/y* rats.

Disclosures: A. Shukla: None. **E. Rivera Melendez:** None. **S.P. Jadhav:** None.

Poster

PSTR044: Social Cognition: Animal Behavior

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.12/O23

Topic: H.06. Social Cognition

Support: SFARI ARC

Title: Hippocampal mechanisms underlying representation of peer locations and trajectories in a social cooperative learning task

Authors: *E. RIVERA MELENDEZ[1], A. SHUKLA[2], J. D. SHIN[3], S. P. JADHAV[4];
[1]Brandeis Univ. Grad. Neurosci. Program, Waltham, MA; [2]Brandeis Univ., Waltham, MA; [3]Neurosci., Brandeis Univ., Somerville, MA; [4]Psychology, Brandeis Univ., Waltham, MA

Abstract: Cooperation is a collective behavior in which interacting partners rely on relevant cues e.g., partner's location or actions, to execute joint actions toward common goals. Yet, the neuronal-circuit mechanisms underlying such complex behavior are unknown. Hippocampal place cells form sequences representing spatial-environment trajectories that are seen during theta oscillations in exploration and as replay during immobility-associated high-frequency network oscillation states known as sharp-wave ripples (SWRs) to support planning of upcoming spatial choices. Importantly, recent work demonstrates that the hippocampal spatial code can also represent the location of other animals. However, it is still unclear what roles these spatial representations of self and others might play in dynamic collective behaviors like cooperation. Here, we aimed to address this gap by conducting high-density neuronal ensemble and local field potential (LFP) electrophysiological recordings in the hippocampus of rats (age: 3-9 mo., strain: Long-Evans, sex: male, N=2) during learning and performance on a novel spatial cooperative behavior paradigm. In this task, rat pairs must coordinate their behavior to obtain food rewards by visiting together complementary maze arms in paired W-shaped mazes and simultaneously nose-poking at reward-wells. Animals alternated between the two complementary mazes across sessions. We found distinct spatial maps of the two mazes in hippocampal place cell populations. As expected, we found that spatial behavior trajectories from the subject's current W-maze environment are replayed during SWR events at reward wells. Interestingly, we also found prevalence of instances in which spatial trajectories from the subject's previous W-maze environment, currently occupied by its partner, are replayed during SWRs. Examining the

proportion of replay events of current versus partner's environments suggests that both environments are prioritized during awake replay to a similar extent. However, it remains to be determined whether a predictive relationship exists between replay content and partner's spatial location. We hypothesize that peer-directed head orientation events can bias replay of self and partner trajectories for planning a coordinated transition to next expected reward well location, thus supporting coordinated behavior. This process can be potentially impaired in Fragile-X KO rats. Taken together, these results suggest that hippocampal physiological patterns may constitute potential mechanisms by which spatial representations of self and others are multiplexed for guiding upcoming cooperative actions.

Disclosures: E. Rivera Melendez: None. **A. Shukla:** None. **J.D. Shin:** None. **S.P. Jadhav:** None.

Poster

PSTR044: Social Cognition: Animal Behavior

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.13/O24

Topic: H.06. Social Cognition

Support: HORIZON-MSCA-2021-PF-01-01

Title: Social cognition in the 22q11.2 Schizophrenia mouse model - does medial prefrontal cortex dopamine and oxytocin fluctuations play a role?

Authors: *C. STUBBENDORFF[1,2], E. KOROBKINA[2], A. BENEDETTI[3], F. PAPALEO[2]; [1]Microtechnology for Neuroelectronics, [2]Genet. of Cognition, ISTITUTO ITALIANO DI TECNOLOGIA, Genova, Italy; [3]Genet. of Cognition, Italian Inst. of Technol., Genova, Italy

Abstract: Schizophrenia is associated with impairment of social cognition. Medial prefrontal cortex (mPFC) is crucial for processing of social cues and regulation of social behaviour. Contextually, both dopamine and oxytocin play a pivotal role in social recognition and social function and inactivation of either oxytocin (OXT) or dopamine (DA) D2 or D3 receptors in mPFC impairs social recognition in mice. 22q11.2 deletion syndrome is one of the largest known genetic risk factors for developing schizophrenia and is associated with impairments to social recognition and emotion processing. The 22q11.2 deletion mouse model (LgDel) displays impairments to social memory and emotion recognition, similar to deficits in patients with schizophrenia. In addition, LgDel mice display altered mPFC neuronal activity patterns during cognitive tests, lower brain OXT levels compared to wild type mice and treatment with DA D2 antagonist rescues social memory deficits in the LgDel schizophrenia model. These findings suggest that social cognitive deficits in schizophrenia could be caused by disruption to mPFC neurocircuitry, possibly mediated by altered DA or OXT availability within mPFC. To examine the relationship between mPFC OXT and DA fluctuations and social cognitive deficits in the LgDel model, wild-type and LgDel mice were injected with a novel OXT or DA biosensor in

mPFC and DA or OXT fluctuations were recorded during a battery of social cognitive tasks. Using this approach, we aim to map the interaction between mPFC OXT, DA and specific aspects of social cognition and cognitive deficits relevant for schizophrenia.

Disclosures: C. Stubbendorff: None. **E. Korobkina:** None. **A. Benedetti:** None. **F. Papaleo:** None.

Poster

PSTR044: Social Cognition: Animal Behavior

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.14/O25

Topic: H.06. Social Cognition

Support: "RAISE - Robotics and AI for Socio-economic Empowerment" and by the European Union - NextGenerationEU.
LgDel-mPFC project HORIZON-MSCA- 2021-PF-01-01 (GA 894032)

Title: Mapping medial prefrontal activity in the LgDel schizophrenia mouse model using chronically implanted SiNAPS CMOS probes

Authors: C. STUBBENDORFF[1], J. F. RIBEIRO[2], G. ORBAN[4], M. VINCENZI[3], A. PERNA[5], G. N. ANGOTZI[5], F. PAPALEO[7], *L. BERDONDINI[6];
[2]NetS3, [3]Microtechnology for Neuroelectronics (NetS3), [1]Inst. Italiano di Tecnologia, Genova, Italy; [4]NeTS3, [5]Microtechnology for Neuroelectronics (NetS3), [6]Fondazione Inst. Italiano di Tecnologia, Genova, Italy; [7]Fondazione Inst. Italiano Di Tecnologia, Genova, Italy

Abstract: Schizophrenia is associated with impairment of social cognition and social function. Medial prefrontal cortex (mPFC) is crucial for processing social cues and regulation of social behaviour. Altered connectivity within mPFC in schizophrenia patients compared to healthy controls could explain patients' poorer ability to differentiate between individuals and impairment to emotion recognition. 22q11.2 deletion syndrome is one of the largest known genetic risk factors for developing schizophrenia and is associated with impairments to social recognition and emotion processing. However, the changes to mPFC neurocircuitry in 22q.11.2 causing the social cognition deficits remain poorly understood. The 22q11.2 deletion mouse model (LgDel) displays impairments to social memory and emotion recognition as well as altered mPFC neuronal activity patterns during cognitive tests. Implantable neural probes based on SiNAPS technology offer the capability of monitoring large brain ensembles at cellular resolution in animal models. Integrating this probe technology in smart systems for behavioural studies in freely moving animals provides an unprecedented opportunity to investigate the electrophysiological correlates of animal behaviour. To this end, we developed a custom platform for chronic SiNAPS recordings and video tracking in freely behaving mice. A custom interconnecting cable is connected from the probe to a commercial commutator, which provides the electrical connectivity to an FPGA-based instrument for data acquisition and device control.

The same FPGA generated control signals for the video cameras, thus ensuring a synchronous recording of neural electrical data and behavioural video data. To explore the relationship between mPFC neuronal activity and synchrony and cognitive deficits in the LgDel mouse, a single-shank 256 electrodes SiNAPS probe was implanted in wild-type and LgDel mice. This allows for recordings of neuronal electrical activity and behaviour to examine genotype dependent differences in state-dependent activity as well as during social and cognitive test. Preliminary results demonstrate the stability for several weeks of recordings collected from chronically implanted SiNAPS probes and of the functionality of acquiring multimodal data from mice. These results pave the way for studies on neurodynamics at the mesoscale in freely moving animals and disease models.

Disclosures: C. Stubbendorff: None. **J.F. Ribeiro:** None. **G. Orban:** None. **M. Vincenzi:** None. **A. Perna:** None. **G.N. Angotzi:** A. Employment/Salary (full or part-time):; Corticale Srl. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Corticale Srl. **F. Papaleo:** None. **L. Berdondini:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Corticale Srl.

Poster

PSTR044: Social Cognition: Animal Behavior

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.15/O26

Topic: H.06. Social Cognition

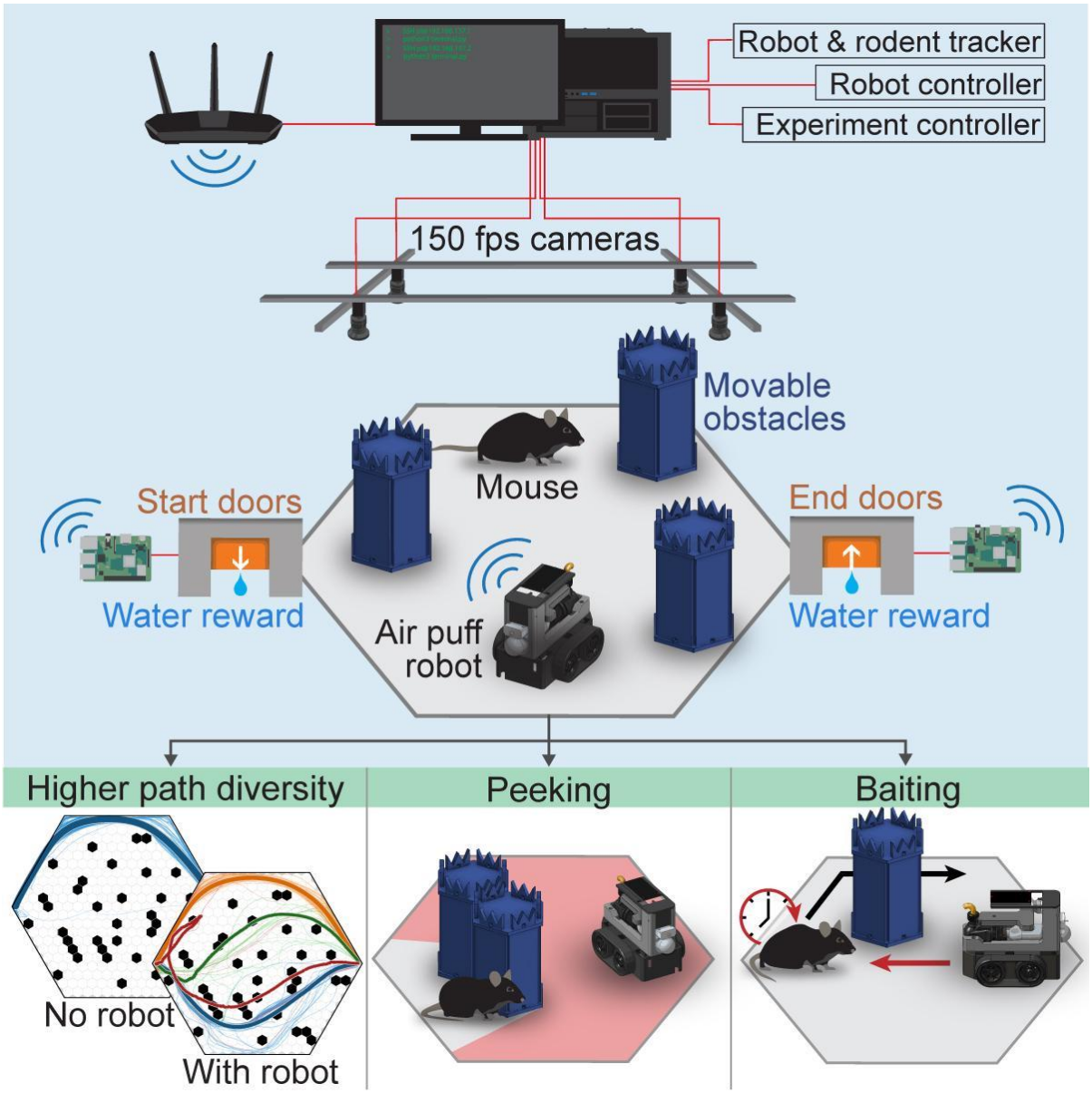
Support: NSF IIS 2123725
NSF ECCS 1835389

Title: A robot-rodent interaction arena with adjustable spatial complexity for ethologically relevant behavioral studies

Authors: *A. LAI[1,2], A. ESPINOSA COARASA[3,1], G. WINK[4,1], C. F. ANGELONI[5,1], D. A. DOMBECK[5,1], M. A. MACIVER[2,4,5,3,1];
[2]Biomed. Engin., [3]Computer Sci., [4]Mechanical Engin., [5]Neurobio., [1]Northwestern Univ., Evanston, IL

Abstract: Outside of the laboratory, animals behave in spaces where they can transition between open areas and coverage as they interact with others. Replicating these conditions in the laboratory can be difficult to control and record. This has led to a dominance of relatively simple, static behavioral paradigms that reduce the ethological relevance of behaviors and may alter the engagement of cognitive processes such as planning and decision-making. Therefore, we developed a method for controllable, repeatable interactions with others in a reconfigurable space. Mice navigate a large honeycomb lattice of adjustable obstacles as they interact with an autonomous robot coupled to their actions. We illustrate the system using the robot as a pseudo-

predator, delivering airpuffs to the mice. The combination of obstacles and a mobile threat elicits a diverse set of behaviors, such as increased path diversity, peeking, and baiting, providing a method to explore ethologically relevant behaviors in the laboratory.



This abstract is from the following work: Lai, A. T., Espinosa, G., Wink, G. E., Angeloni, C. F., Dombeck, D. A., & MacIver, M. A. (2024). A robot-rodent interaction arena with adjustable spatial complexity for ethologically relevant behavioral studies. Cell reports, 43(2), 113671. https://doi.org/10.1016/j.celrep.2023.113671

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Poster

PSTR044: Social Cognition: Animal Behavior

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.16/O27

Topic: H.06. Social Cognition

Title: Social Calculus In Mice: Decoding Mice Behavior in a Reward Trade-off Task

Authors: E. TURE[1], D. KVITSIANI[2], *E. DEMIR[1];
[2]Anat., [1]Southern Illinois Univ., Carbondale, IL

Abstract: Organisms have evolved neural processes that help them collect, evaluate, and use social information to make decisions, particularly when selecting potential mates. These processes are crucial for understanding social valuation within the context of various neurodevelopmental disorders that lead to social impairments, yet their mechanisms remain unclear. In this presentation, we introduce a behavioral framework designed to conduct thorough and comprehensive analyses of social behaviors in mice. This innovative framework also sheds light on the fundamental neurobiological principles of social cognition and its variations in conditions such as autism spectrum disorder.This mouse behavioral task, drawing on principles from psychophysical research and game theory, assesses their social preferences when choosing between social and non-social rewards. In this setup, a thirsty mouse navigates between a water dispenser and a rotating carousel with several chambers. Each chamber may contain a mouse from the same or a different strain, a mouse lacking gender specific pheromones, or be empty. As the carousel rotates and pauses, it aligns one chamber directly in the mouse's path, facilitating an interaction with a potential social partner. The mouse must then weigh the time spent engaging with the social cue against the need to drink water, balancing its social interests with its physiological needs. This arrangement enables us to gauge the significance mice assign to social interactions compared to a basic need, termed here as 'water currency', by observing how they prioritize social engagement over water access.Furthermore, our 'Reward Trade-off Task' offers a quantifiable, standardized method to assess social value, adjustable by altering the water quantity. Moving forward, our plans include probing the neurobiological bases of how social values are formed, as well as exploring how phenotypic traits influence individual mice's social preferences, through the integration of neurophysiological data and optogenetic techniques.

Disclosures: E. Ture: None. **D. Kvitsiani:** None. **E. Demir:** None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.01/Web Only

Topic: H.08. Learning and Memory

Title: Mixed signatures for subcritical dynamics in rodent hippocampus during sleep and awake epochs

Authors: *P. GARG;
All India Inst. of Med. Sciences, Rishikesh, Rishikesh, India

Abstract: In complex physical systems, the observed macroscopic behavior requires evaluation of the interaction between its constituents. The underlying dynamics between these constituents often lead to transitions between states and are widespread among natural systems such as water boiling or freezing, earthquakes, or atmospheric precipitation. Similar dynamics are also observed in the brain. This phenomenology following precise mathematical formulation in statistical physics is referred to as criticality. It is marked by the transition between disordered (subcritical) and ordered states (supercritical). Brain criticality has recently been attributed to optimal information processing and information flow. It posits that the brain operates near critical to the critical point, although the field is rife with controversies and contrasting evidence. Similar computational capacities are also observed during sharp wave ripples in the hippocampus prompting the need to correlate their dynamics. To evaluate criticality, avalanche metrics, branching metrics, and time series metrics were computed with hippocampal local field potential recordings from mice during ripple and no ripple times, throughout awake and sleep epochs. In the current study, neuronal avalanches, branching process, crackling noise relation, deviation from criticality coefficient, and Hurst exponents for long-range temporal correlations are reported. The computed metrics indicate mixed subcritical to critical dynamics in the hippocampus and minimal difference between ripple and no ripple times across measured metrics. These findings support that criticality and sharp wave ripples are possibly distinct dynamical properties, criticality being more fundamental in nature. It also suggests the possibility that criticality may not significantly optimize information processing, particularly during ripples in the hippocampus. Previously, subcriticality has been associated with focused attention, response specificity to stimulus, and stimulus detection among others as compared to supercriticality. The dominance of subcriticality over supercriticality is also said to control brain activity from becoming epileptic. While it’s suggested that the hippocampus operates closer to criticality during expensive cognitive tasks, the reported findings indicate the likelihood of subcritical to near critical dynamics during less demanding tasks in contrast to cortical structures. Overall, the evidence demonstrates heterogeneity in signatures of criticality among animals and brain areas, indicating the presence of broad-range neuronal dynamics.

Disclosures: P. Garg: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.02/O28

Topic: H.08. Learning and Memory

Support: NIH R01MH124870

Title: Somatostatin-expressing stratum oriens interneurons form biased circuits with deep and superficial pyramidal cells in CA1 hippocampus

Authors: *A. JOHANTGES, A. SAFA, A. MARSHALL, E. PAYNE, M. HANSON, J. C. WESTER;
Dept. of Neurosci., Ohio State Univ., Columbus, OH

Abstract: Pyramidal cells (PCs) in CA1 serve as the major output of hippocampal computations. Recent work has found that these cells are not homogenous and can be divided into two subpopulations based on their radial position. Deep PCs (dPCs) and superficial PCs (sPCs) express different genes, have different electrophysiological properties, and engage in separate aspects of spatial memory processing. Furthermore, dPCs and sPCs also form biased circuits with inhibitory interneurons (INs), including parvalbumin (PV+) and cholecystokinin (CCK+)-expressing basket cells. These cell-type-dependent inhibitory circuits are likely necessary for differential information processing of dPCs and sPCs. Another major class of INs include somatostatin-expressing (SST+) cells, whose somas mostly reside within the stratum oriens (SO). SST+ INs include OLM and bistratified cells that innervate the apical and proximal dendrites of PCs, respectively. It is unknown whether dPCs or sPCs form biased circuits with these dendrite-targeting SST+ INs. To address this, we used a combination of dual whole-cell patch clamp electrophysiology and optogenetic-assisted circuit mapping in slices of CA1. First, we used paired recordings to assess the connectivity and strength of synapses from PCs to SST+ INs. We performed these experiments in both Nkx2.1-cre;Ai14 and 5HT3A-GFP mice because previous work suggests they label distinct subpopulations of SST+ INs. Strikingly, we found that sPCs provide synaptic connections to SST+ INs (both OLM and bistratified cells) at a higher rate than dPCs, but only for those labeled in Nkx2.1-cre;Ai14 mice. Connectivity rates from sPCs and dPCs to SST+ INs were comparable using 5HT3A-GFP mice. Thus, SST+ INs from these two mouse lines may engage in distinct circuit functions. Next, we used optogenetics to investigate synaptic input from SST+ INs to dPCs and sPCs. We injected an AAV encoding floxed channelrhodopsin into the SO of ventral CA1 in SST-Cre mice. We recorded pairs dPCs and sPCs while optogenetically stimulating SST+ INs. These experiments revealed that a subpopulation of dPCs receive stronger SST+ IN innervation than all other PCs. Thus, our data suggest that SO INs are preferentially innervated by sPCs in a subtype-specific manner and then preferentially inhibit the activity of a specific population of dPCs.

Disclosures: A. Johantges: None. **A. Safa:** None. **A. Marshall:** None. **E. Payne:** None. **M. Hanson:** None. **J.C. Wester:** None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.03/O29

Topic: H.08. Learning and Memory

Title: Neural Control Of Hippocampus-Dependent Memory Consolidation During Sleep

Authors: *M. XU;
Inst. of Neurosci., Chinese Acad. of Scie, Shanghai City, China

Abstract: The hippocampus plays a crucial role in memory consolidation during sleep. However, the exact cell types controlling this process are largely unknown. Here, we identified a new type of GABAergic interneuron (GINX) in the hippocampus that is selectively active during non-rapid eye movement (NREM) sleep, which is the major sleep state for memory consolidation. Inhibiting the activity of GINX neurons during NREM sleep impaired the formation of hippocampus-dependent spatial memory. Furthermore, GINX neurons had widespread projections within the hippocampus and controlled the generation of sharp-wave ripple activity, a hippocampal neural signature for memory reactivation. Together, we have uncovered a potential key cell type in the control of hippocampus-dependent memory consolidation.

Disclosures: M. Xu: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.04/O30

Topic: H.08. Learning and Memory

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COLE Neuroscience Research Awards to XC
UNH CoRE PRP to XC
UNH summer TA research fellowship(STAF) to JW, YZ
UNH Dissertation Year Fellowship (DYF) to YZ

Title: Nmda receptors control neural activity hierarchy: loss of control of hierarchy leading to learning impairments, dissociation, and psychosis

Authors: *L. WANG[1], Y. ZHOU[2], J. GLENN WIXSON[3], J. TORPEY[3], L. QIU[3], M. LYON[4], X. CHEN[3];
[1]1Department of Mol., Cell., and Biomed. Sci., Univ. of New Hampshire, Durham, NH; [2]Boston

Univ., Boston, MA; [3]Dept. of Mol., Cell., and Biomed. Sci., Univ. of new Hampshire, Durham, NH; [4]Mathematics and Statistics, Univ. of New Hampshire, Durham, NH

Abstract: While it is known that associative memory is preferentially encoded by memory-eligible "primed" neurons, real-time neural activity hierarchy has not been quantitatively determined and little is known about how such a hierarchy is established. Leveraging *in vivo* calcium imaging of hippocampal neurons on freely behaving mice, we developed the first method to quantify real-time neural activity hierarchy in the CA1 region. Neurons on the top of activity hierarchy are identified as primed neurons. In primary cilia knockout mice that exhibit severe learning deficits, the percentage of primed neurons is drastically reduced. To examine how an activity hierarchy is formed, we developed a simplified neural network model that incorporates simulations of linear and non-linear weighted conductance, modeling the synaptic ionic contributions of AMPA and NMDA receptors, respectively. We found that moderate non-linear to linear conductance ratios naturally leads a small fraction of neurons to become more active than others. Removal of the non-linear conductance eliminates an existing activity hierarchy and reintroducing it back to the network stochastically primes a new pool of neurons. Experimentally, blockade of NMDA receptors by ketamine not only temporarily decreases general neuronal activity causing learning impairment, but also disrupts the existing neural activity hierarchy. Together, this study develops a unique method to measure neural activity hierarchy for associative learning and identifies NMDA receptors as a key factor that controls the hierarchy. It presents the first evidence suggesting that hierarchy disruption by NMDA receptor blockade, at least in part, accounts for dissociation and psychosis.

Disclosures: L. Wang: None. **Y. Zhou:** None. **J. Glenn Wixson:** None. **J. Torpey:** None. **L. Qiu:** None. **M. Lyon:** None. **X. Chen:** None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.05/O32

Topic: H.08. Learning and Memory

Support: NRF-2012R1A3A1050385
SSTF-BA1602-11
NRF-2020R1A2C2007285

Title: In vivo dynamics of hippocampal fear engram synapses in different memory states

Authors: *C. LEE[1], B. LEE[2], H. JUNG[3], C. LEE[1], Y. SUNG[1], H. KIM[4], J. KIM[5], J. SHIM[6], J.-I. KIM[4], D. CHOI[1], H. PARK[7], B.-K. KAANG[8];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Dept. of Chem. and Chem. Biol., Harvard Univ., Cambridge, MA; [3]Inst. for Basic Sci. (IBS), Daejeon,, Korea, Republic of; [4]Dept. of Biol. Sci., SNU Med. Library, Seoul, Korea, Republic of; [5]Seoul Natl. Univ., Seoul-si, Korea, Republic of;

[6]Dept. of Physics and Astronomy, SNU Physics and Astronomy, Seoul, Korea, Republic of;
[7]Dept. of Electrical and Computer Engin., Univ. of Minnesota, Twin Cities, Minneapolis, MN;
[8]Sch. of Biol. Sci., Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract: Synaptic ensembles which are the key components of brain networks underly cognitive functions including learning and memory. The formation of contextual fear memory is known to lead to an increase in synaptic density among engram cells in these synaptic engrams. Further examination on the CA3-CA1 engram synapses demonstrated larger spine head diameters, indicating a correlation between the strength of memory and the degree of synaptic connection (Choi et al., 2018). For a further understanding of the dynamics of synapse between CA3 and CA1, we tracked identical synapses across multiple time points by applying dual-eGRASP technique to *in vivo* two-photon imaging. Contextual fear memory formation led to enhanced synaptic connections between engram neurons and significant synaptogenesis within the hippocampus network. While only 4.6% of E-N synapses were generated, 20% of E-E synapses were newly formed due to memory formation. Conversely, the disappearance of CA3 engram to CA1 engram (E-E) synapses was particularly correlated to extinction learning (Kolmogorov-Smirnov test, extinction, p=0.0039; no extinction, p=0.7305). Moreover, synaptic engrams within the CA3-CA1 circuit were significantly clustered after fear memory formation, due to the addition of new synapses nearby pre-existing synaptic connections. Overall, we conclude that the key sites for alterations across fear memory states are the synaptic engrams between CA3 and CA1.

Disclosures: C. Lee: None. **B. Lee:** None. **H. Jung:** None. **C. Lee:** None. **Y. Sung:** None. **H. Kim:** None. **J. Kim:** None. **J. Shim:** None. **J. Kim:** None. **D. Choi:** None. **H. Park:** None. **B. Kaang:** None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.06/O33

Topic: H.08. Learning and Memory

Support: JST ERATO (JPMJER1801)
JSPS Grants-in-Aid for Scientific Research (22K21353)
AMED CREST (22gm1510002h0002)

Title: Discrimination task of direct electrical stimulation of rat hippocampus

Authors: *S. TANAKA[1], N. MATSUMOTO[2,3], Y. IKEGAYA[2,3];
[1]Univ. of Tokyo, Tokyo, Japan; [2]Grad Sch. Pharmaceut Sci., The Univ. of Tokyo, Tokyo, Japan;
[3]Institute for AI and Beyond, The University of Tokyo, Tokyo, Japan

Abstract: Access to the external environment through the senses is essential for animals to determine their behavior. For example, they rely on their sense of smell to find food and their

sense of sight to recognize their surroundings. The functions of cortical regions are subdivided, and sensory information is represented in corresponding brain regions. Experimentally, electrical stimulation of a specific sensory region can produce the corresponding "artificial" sensation. As a pioneering example of this application, our previous work has shown that geomagnetic information can be transmitted by electrical stimulation to the somatosensory cortex of mice to achieve spatial navigation based on the surrounding geomagnetic fields. However, to date, behavioral tasks using such artificial electrical stimulation have mainly involved stimulation of primary sensory cortices, and it is not known whether electrical stimulation of higher-order brain regions can also be used for discrimination tasks. We focused on the hippocampus as a candidate for such higher brain regions. The hippocampus contains place cells that encode spatial information. Although these cells do not directly represent sensory information, they are fundamental to the representation of the external environment. Therefore, we hypothesized that rats would be able to discriminate between electrical stimulation of the hippocampus and sensory cortex. In the current experiment, rats with stimulating electrodes implanted into both hippocampi were placed in a box with two levers. The rats were trained to press the right lever when the right hippocampus was stimulated and the left lever when the left hippocampus was stimulated, and the medial forebrain bundle (MFB) was stimulated as a reward for each correct choice. This study provides the first evidence that rats can utilize their hippocampal neural activity for task-based discrimination.

Disclosures: **S. Tanaka:** None. **N. Matsumoto:** None. **Y. Ikegaya:** None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: MCP Hall A

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Program #/Poster #: PSTR045.07/O34

Topic: H.08. Learning and Memory

Support: IBS-R002-A1; M.W.J.

Title: Dynamics of value-dependent hippocampal neuronal activity during learning

Authors: *J. SHIN[1,2], Y. JEONG[1,2], M. JUNG[1,2];
[1]Korea Advanced Inst. in Sci. and Technol., Daejeon, Korea, Republic of; [2]Institute For Basic Science, Daejeon, Korea, Republic of

Abstract: Although a growing body of evidence indicates the involvement of the hippocampus in processing value-related signals, many aspects of hippocampal value processing remain to be characterized. To investigate the dynamics of hippocampal value signals during learning, we monitored value-dependent hippocampal neuronal activity over the course of place-value association learning. Employing calcium imaging, we examined the activity of dorsal CA1 neurons during a spatial forced-choice task in which mice visited three arms delivering water rewards with varying probabilities (10%, 50%, and 90%) in random order over three daily

sessions. On the third day, consistent with previous research, we found that the activity of putative pyramidal neurons tends to increase as reward probability increases when the animal approaches the rewarding site. On the contrary, during departure from the rewarding site, place cells tended to decrease their activity as reward probability increases. Additionally, we identified synchronous discharges of CA1 neurons during immobile periods, and if place cells showed sequential activity according to their place field locations, we considered them as putative replays of spatial trajectories. This analysis indicated that the putative replay of outbound trajectory tends to be more frequent as reward probability increases on the first day. These results indicate that the dorsal CA1 place cells show value-dependent activity during both mobile and immobile periods, and that such value-dependent firing varies dynamically as learning progresses. It remains to be determined how these dynamic value-dependent activities relate to hippocampal mnemonic functions.

Disclosures: J. Shin: None. **Y. Jeong:** None. **M. Jung:** None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

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Topic: H.08. Learning and Memory

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Title: Novel dynamic autocorrelation measure (dAC) uncovers time-dependent changes in the organization of neural timescales along the hippocampal long axis

Authors: *L. HOMANN[1], A. GOLESTANI[2,3,4], N. R. BOUFFARD[5], M. MOSCOVITCH[1,6], M. D. BARENSE[1,6];
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Dept. of Physics and Astronomy, [3]Hotchkiss Brain Inst., [4]Dept. of Oncology, Univ. of Calgary, Calgary, AB, Canada; [5]Dept. of Psychological and Brain Sci., Washington Univ. in St. Louis, St. Louis, ON, Canada; [6]Rotman Res. Inst. at Baycrest, Toronto, ON, Canada

Abstract: To support cognition during continuous multimodal experience, information is accumulated and integrated over multiple timescales throughout the brain in a topographical profile that reflects the functional and representational specializations of different cortical regions. These neuronal timescales can be indexed using temporal autocorrelation, a measure of signal stability over time. While autocorrelation in fMRI is conventionally estimated using the

entire length of the BOLD timecourse, thus assuming that autocorrelation profiles are static, research has found that autocorrelation can change depending on brain state and task demands. These findings underscore the critical need to develop a method of assessing how autocorrelation changes dynamically, over shorter timescales. To address this gap, we introduce a novel measure termed dynamic autocorrelation (dAC), which employs a sliding window approach to compute single-voxel autocorrelation using brief blocks of fMRI signals. Using this new method, we investigated two objectives using a resting state dataset from the Human Connectome Project. First, we aimed to replicate the profile of hippocampal autocorrelation found in our past work that estimated autocorrelation over the entire length of the BOLD timecourse (Bouffard, Golestani, et al., 2023; Coughlan et al., 2023). Consistent with prior findings, when dAC values were averaged across time, autocorrelation was higher in the anterior-medial region of the hippocampus as compared to the posterior-lateral region. Second, we sought to determine whether this hippocampal autocorrelation profile was stable across time. Interestingly, we found that when considering autocorrelation on shorter timescales this profile was only replicated in 56 to 57% of time windows on average. In the remaining time windows, the autocorrelation profile was reversed, such that autocorrelation was higher in the posterior-lateral region of the hippocampus as compared to the anterior-medial region. Therefore, autocorrelation profiles exhibit dynamic fluctuations over time across the hippocampal long axis. Overall, this work paves the way for future research to investigate how neural timescales adapt to rapid environmental changes in a manner not previously achievable.

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Poster

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Title: Exploring neural correlates of categorization learning in hippocampus

Authors: *L. SAINZ VILLALBA[1,2], R. BOEHRINGER[3], B. F. GREWE[4];
[1]Inst. of Neuroinformatics, Zurich, Switzerland; [2]ETH Zurich, Zurich, Switzerland; [3]Inst. for Neuroinformatics, ETH Zurich, Zürich, Switzerland; [4]ETH Zurich, Zuerich, Switzerland

Abstract: Animals and humans acquire knowledge through experience in a way that allows them to rapidly and flexibly generalize to novel situations. Several findings suggest that the Hippocampus (HC) is involved in the development of this type of conceptual learning beyond navigational context, including non-spatial variables if relevant to a task. However, how concepts and categories arise and how the hippocampus is involved in building these from episodic memories still remains unknown. To study this process, we trained mice on a binary categorization task of auditory pure tones through different learning phases. Categorization depended on frequency and consisted of a linear split (boundary) between low and high frequencies. To perform successfully, mice had to learn the category membership of a given tone from experienced history of exemplars. To investigate the role of HC, we used 2-photon Ca2+ imaging to record at the initial discrimination training phase (one stimulus per category), at categorization training (with many more stimuli per category) and, at generalization tests after each. Interestingly, after being trained in the first discrimination task, mice fail to classify correctly novel stimuli far from the boundary between categories in the generalization test, which is surprising compared to what is expected from psychophysical curves or simple machine learning classifiers. However, this generalization ability did improve in the second test after categorization training. To further understand these differences we studied neural activity, finding that single neuron responses showed responsiveness to relevant task variables: category, choice and outcome as well as combinations of those. Since these showed high heterogeneity, we used population activity analysis, using linear decoders (SVMs), that confirmed significant choice and outcome information available at different timepoints within the trial. Additionally, the geometry of these variables, i.e. how disentangled is the neural representation, analyzed with cross variable decoding, revealed that choice was encoded in a factorized way respect to outcome (abstract). These neural population properties regarding choice and outcome appear to stay stable across the different learning phases providing episode encoding in the appropriate format for other areas to learn from history. In this experiment we present a categorization paradigm with two distinct learning phases and corresponding generalization tests to investigate the learning of a category structure from a history of exemplars when a simple association strategy, as in a look-up table, is challenged to successfully perform the task.

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Poster

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Topic: H.08. Learning and Memory

Support: HHMI
NIH 1R01 MH135576

Title: Dendrite-targeting OLM interneurons regulate the formation of experience-dependent CA1 representations.

Authors: E. CAMPBELL[1], L. MARTIN[2], J. C. MAGEE[1], *C. GRIENBERGER[2];
[1]Neurosci., HHMI/Baylor Col. of Med., Houston, TX; [2]Brandeis Univ., Waltham, MA

Abstract: Spatial learning requires the experience-dependent development of place cell representations in hippocampal area CA1. Previous results demonstrate that a non-Hebbian type of synaptic plasticity, behavioral timescale synaptic plasticity (BTSP), has a fundamental role in novel place cell formation. BTSP is initiated by dendritic calcium plateau potentials triggered in the distal tuft region of CA1 pyramidal neurons. Our current working model suggests that these plateau potentials arise from the interaction between a target signal (known to be provided by excitatory input from the entorhinal cortex) and an inhibitory feedback source representing the current state of the CA1 representation. However, the source of this inhibitory feedback involved in BTSP remains undescribed. A potential candidate neuronal subtype are the oriens lacunosum-moleculare (OLM) interneurons, which primarily receive feedback excitation from the local CA1 population and form synapses onto CA1 pyramidal neuron tuft dendrites. Here, we used *in vivo* two-photon somatic and axonal calcium imaging to record the activity of somatostatin (SST)-expressing OLM interneurons in mice exploring a novel linear track for the first time. After correcting for the spatial profile of the animals' running speed, we found that OLM activity aligns well with the inhibitory feedback predicted by the BTSP model. Thus, their activity increased as a function of learning, with a higher relative activity increase around the reward site. Further, a subset of OLM interneurons that express the nicotinic receptor alpha 2 subunit (Chrna2α) have activity comparable to the larger SST-expressing OLM interneuron population and provide highly specific genetic access to inhibitory feedback in CA1. These results suggest that the OLM interneurons may constitute the feedback inhibitory element regulating BTSP induction. Ongoing optogenetic manipulations of Chrna2α OLM activity and the CA1 feedback causally test this hypothesis. Taken together, our results point toward dendrite targeting OLM interneurons as a central signal regulating the BTSP-mediated shaping of CA1 representations during learning.

Disclosures: E. Campbell: None. **L. Martin:** None. **J.C. Magee:** None. **C. Grienberger:** None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

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Program #/Poster #: PSTR045.11/P1

Topic: H.08. Learning and Memory

Support: HHMI

Title: Plasticity improves stability: How representational drift provides robustness to synaptic perturbations and continual learning

Authors: *M. NATRAJAN[1], J. E. FITZGERALD[2];
[1]Northwestern Univ., Johns Hopkins Univ., Chicago, IL; [2]Neurobio., Northwestern Univ., Evanston, IL

Abstract: Memories are believed to be stored in synapses and retrieved through the reactivation of neural ensembles. Learning new memories alters synaptic weights, potentially eroding previously stored memories sharing those synapses. This poses the continual learning challenge of preserving old memories while assimilating new ones. Perhaps relatedly, neural representations exhibit extensive dynamics, even in the absence of overt behavioral changes associated with those representations, a phenomenon known as representational drift. Here, we show that representational drift can steer the network towards a robust regime that fosters continual learning. This active facilitation of memory maintenance complements previous proposals that representational drift results from new learning. We modeled representational drift as a diffusion in the solution space of synaptic weights that satisfy specific input-output mappings. Our network used a clipped threshold linear activation function, wherein numerous input currents correspond to inactive and saturated neurons. Consequently, when large weights are allowed, numerous synaptic weights produce sparsely engaged representations with mostly inactive and saturated neurons. Furthermore, weight perturbations have less impact on the activity of inactive and saturated neurons, making sparsely engaged representations robust to weight changes. Thus, representational drift tends to favor sparsely engaged, robust representations. However, these robust solutions hinder new learning by generating sparsely engaged representations that lack gradients, thus trapping the system in local optima. Conversely, densely engaged initializations facilitate learning but yield non-robust solutions, creating a learnability-robustness tradeoff. Representational drift paired with an allocation procedure can effectively transcend this learnability-robustness tradeoff. To facilitate new learning, we reallocate weights to generate densely engaged representations for the new input condition. This is followed by learning, and then by representational drift, which moves the system from the high-learnability regime to the robust regime. Learning and allocation introduce weight perturbations for previously stored memories. However, representations achieved through drift exhibit enhanced robustness, resulting in less degradation compared to those acquired without representation drift. Synaptic diffusion and representational drift in between learning events can thus be leveraged to ameliorate the continual learning problem.

Disclosures: **M. Natrajan:** None. **J.E. Fitzgerald:** None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

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Topic: H.08. Learning and Memory

Support: STI2030-Major Projects
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Shanghai Municipal Health Commission

Title: Neuropeptide Y co-opts neuronal ensembles for memory lability and stability

Authors: *Y. WU[1], W.-G. LI[4], T.-L. XU[2,3];
[1]Discipline of Neurosci. and Dept. of Anat. and Physiol., Shanghai Jiao Tong Univ. Sch. of Med., Shanghai City, China; [2]Discipline of Neurosci. and Dept. of Anat. and Physiol., [3]Shanghai Jiao Tong Univ. Sch. of Med., Shanghai, China; [4]Inst. of Med. Science, Shanghai Jiao Tong U, Shanghai, China

Abstract: Memory engrams are formed by activity-dependent recruitment of distinct subsets of excitatory principal neurons (or neuronal ensembles) whereas inhibitory neurons pivot memory lability and stability. However, the molecular logic for memory engrams to preferentially recruit specific type of interneurons over other subtypes remains enigmatic. Using activity-dependent single-cell transcriptomic profiling6-8 in mice with training of cued fear memory and extinction, we discovered that neuropeptide Y (NPY)-expressing (NPY+) GABAergic interneurons in the ventral hippocampal CA1 (vCA1) region exert fast GABAergic inhibition to facilitate the acquisition of memory, but bifurcate NPY-mediated slow peptidergic inhibition onto distinct sub-ensembles underlying the extinction of single memory trace. Genetically encoded calcium and NPY sensors revealed that both calcium dynamics of NPY+ neurons and their NPY release in vCA1 ramp up as extinction learning progresses while behavioral state switches from “fear-on” to “fear-off”. Bidirectional manipulations of NPY+ neurons or NPY itself demonstrated NPY is both necessary and sufficient to control the rate and degree of memory extinction by acting on two physically non-overlapping sub-ensembles composed of NPY1R- and NPY2R-expressing neurons. CRISPR/Cas9-mediated knockout of NPY2R or NPY1R further unravels that NPY co-opts its actions on these two sub-ensembles to gate early fast and late slow stages of extinction. These findings exemplify the intricate spatiotemporal orchestration of slow peptidergic inhibitions from single subtype of GABAergic interneurons to fine-tune engram lability verse stability of memory.

Disclosures: **Y. Wu:** None. **W. Li:** None. **T. Xu:** None.

Poster

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Program #/Poster #: PSTR045.13/P3

Topic: H.08. Learning and Memory

Support: 310030_205198

Title: Environmental enrichment promotes sparse coding in hippocampus via increased dendritic inhibition

Authors: *E. VERDIYAN, S. KOUVAROS, J. BISCHOFBERGER;
Dept. of Biomedicine, Univ. of Basel, Basel, Switzerland

Abstract: Environmental enrichment improves hippocampus-dependent spatial learning and memory. However, how enrichment influences hippocampal network activity remains still largely unclear. Using cFos labeling, we showed that exploration of a novel context leads to increased cFos activity in hippocampal principal neurons in mice housed under both standard and enrichment conditions. Remarkably, the number of cFos-expressing cells was lower in enriched mice. Additionally, we recorded Ca^{2+} responses in CA1 pyramidal cells (PCs) using miniature microscope in mice performing spatial exploration. We observed lower event frequency in PCs of enriched mice. It indicates that enrichment does not increase principal cell activity but promotes sparse coding in hippocampus. Next, we asked how enrichment affects GABAergic inhibition. We found that enrichment leads to increased activation of dendrite-targeting somatostatin-expressing (SOM) interneurons during exploration due to larger number of glutamatergic synapses onto SOM interneurons. It is accompanied by increased synaptic transmission between PCs and SOM interneurons, as shown by whole-cell patch-clamp recordings in SOM interneurons. Furthermore, we observed increased lateral feedback inhibition in enrichment. To understand how it translates *in vivo*, we performed simultaneous Ca^{2+} imaging from CA1 PCs and optogenetic silencing of SOM interneurons in mice during exploration. We found that SOM interneurons have a big impact on the event frequency of PCs and the number of active cells. Most importantly, the effect of silencing on the number of active cells was stronger in enrichment. Taken together, our data show that environmental enrichment decreases the size of hippocampal cell assemblies via enhanced recruitment of dendrite-targeting SOM interneurons. It leads to sparse coding, which may increase memory capacity and minimize interference between memory items, providing an advantage for hippocampal processing.

Disclosures: E. Verdiyan: None. **S. Kouvaros:** None. **J. Bischofberger:** None.

Poster

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Topic: H.08. Learning and Memory

Support: DFG CRC 779
DFG CRC 1436

Title: Phase-locking of hippocampal CA3 neurons to distal CA1 theta oscillations selectively predicts memory performance

Authors: *M. YOSHIDA[1,2,3], S.-P. KU[4], E. ATUCHA[4], H. MULLA-OSMAN[4], R. KAYUMOVA[5], J. L. CSICSVARI[6], M. SAUVAGE[7];
[1]LIN Magdeburg, Magdeburg, Germany; [2]DZNE Magdeburg, Magdeburg, Germany; [3]Center for

Behavioral Brain Sciences, Magdeburg, Magdeburg, Germany; [4]Functional Architecture of Memory, Leibniz Inst. for Neurobio., Magdeburg, Germany; [5]FAM, Leibniz Inst. for Neurobio., Magdeburg, Germany; [6]Inst. of Sci. and Technol. (IST) Austria, Klosterneuburg, Austria; [7]Functional Architecture of Memory Dpt, Leibniz Inst. for Neurobio., Magdeburg, Germany

Abstract: How the coordination of neuronal spiking and brain rhythms between hippocampal subregions supports memory function remains elusive. We studied the interregional coordination of CA3 neuronal spiking with CA1 theta oscillations by recording electrophysiological signals along the proximodistal axis of the hippocampus in rats that were performing a high memory demand recognition memory task adapted from humans. We found that CA3 population spiking occurs preferentially at the peak of distal CA1 theta oscillations when memory was tested but only when previously encountered stimuli were presented. In addition, decoding analyses revealed that only population cell firing of proximal CA3 together with that of distal CA1 can predict performance at test in the present non-spatial task. Overall, our work demonstrates an important role for the synchronization of CA3 neuronal activity with CA1 theta oscillations during memory test.

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Poster

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Support: NIH Grant 1U19NS132720-01
NIH Grant 1K99NS135650-01

Title: Electron microscopy reconstruction of a hippocampal CA3 volume

Authors: *Z. ZHENG[1], R. LU[1], D. W. TANK[1], H. SEUNG[2];
[1]Princeton Univ., Princeton, NJ; [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: The CA3 region within the hippocampus is believed to be instrumental in memory storage and retrieval. The cellular substrates in CA3 underlying these functions include excitatory pyramidal cells with extensive recurrent collaterals and a great diversity of inhibitory cells. Here we presented 3D electron microscopy (EM) reconstructions of the hippocampal CA3 at synaptic resolution. The EM data is acquired using high-throughput beam deflection transmission electron microscopes (TEMs) equipped with serial-section GridTape technology. The xy resolution of the dataset is 3 nm per pixel with a nominal section thickness of 40 nm. The volume is divided into two separate parts, measuring 0.87 x 1 x 0.083 mm^3 and 0.87 x 1 x 0.049 mm^3, respectively. The automated reconstruction includes segmentation, synapse detection, and semantic labeling such as soma, axons, dendrites, and glia. Our analysis of the dense

reconstructions aims to relate the pattern of neural connectivity to morphologically defined cell types in CA3, thereby constraining circuit models of learning and memory. Acknowledgement - Zetta AI for reconstruction.

Disclosures: Z. Zheng: None. **R. Lu:** A. Employment/Salary (full or part-time):; Zetta. **D.W. Tank:** None. **H. Seung:** A. Employment/Salary (full or part-time):; Zetta.

Poster

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Topic: H.08. Learning and Memory

Support: 5R01MH101297-10
T32MH067564

Title: An organizedrepresentation of a non-sequentially experienced space in the hippocampus.

Authors: *G. TOCKER[1], J. Y. OH[2], F. XUAN[3], D. A. DOMBECK[4];
[1]Northwestern Univ., Evanston, IL; [2]Northwestern Univ., Evanston, CA; [3]Dept. of Neurobio., Northwestern Univ., Evanston, IL; [4]Neurobio., Northwestern Univ., Evanston, IL

Abstract: Learning new memories and navigating the world are essential for humans and animals. Two seminal findings relate both functions to the hippocampus. In humans and rodents, the hippocampus is necessary for forming new episodic memories and, in rodents, hippocampal neurons encode a spatial map of their environment through sequential firing of place cells. A way to bridge the gap between these functions is to consider the hippocampus as a sequence generator that encodes experiences in the temporal order in which they are experienced. A large body of research has focused on how the hippocampus encodes sequential stimuli and events. It remains unclear, however, whether the hippocampus can build an organized map of continuous spaces when the elements of those spaces are not sequentially experienced. We developed a behavioral task where mice must discriminate between the height of objects to receive reward. Importantly, the objects of different height were presented randomly rather than sequentially according to height. While the mice performed the task, we imaged CA1 neural activity and compared it to a control group of mice that passively viewed the objects. We found a representation of objects' heights in both the passively viewed mice group and the active task mice group. However, in the active task, the representation was organized such that the population vectors representing more similar heights were closer to each other in state space than they were to the vectors representing dissimilar heights. This organization was not observed in the passive task. This suggests a reorganization of the hippocampal height representation in a task-specific manner. The height variable was encoded not through sequential firing codes, but through cells that fired in response to multiple heights. To explore how the representation organization relates to task variables, we created a behavioral model that fits the hierarchy

between different heights (height representation) to best predict animal behavior. When we compared the relation between the height representation from the behavioral model and the height representation from the neural population vectors, we found significant correlations between them. These results demonstrate that the hippocampus can form relations to map spaces whose elements were not sequentially experienced. This mapping was learning dependent, since learning the behavioral task reorganized the stimuli representations into a task-relevant structure.

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Poster

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Support: NIH Grant 5F32MH123003
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Title: Hippocampal cellular assembly activity during remote representation neurofeedback

Authors: *M. E. COULTER[1], A. GILLESPIE[2], J. CHU[3], E. L. DENOVELLIS[4], B. SHARMA[5], X. DENG[6], U. EDEN[7], C. KEMERE[8], L. M. FRANK[9];
[1]Ctr. for Integrative Neurosci., Univ. of California San Fransisco, San Francisco, CA; [2]Biol. Structure, Univ. of Washington, Seattle, WA; [3]Electrical and Computer Engin., Rice Univ., Huntington Beach, CA; [4]UCSF, HHMI, San Francisco, CA; [5]Univ. of California San Francisco, San Francisco, CA; [6]Statistics, Columbia Univ., New York, NY; [7]Mathematics and Statistics, Boston Univ., Boston, MA; [8]Rice Univ., Houston, TX; [9]Departments of Physiol. and Psyciatry, UC San Francisco, San Francisco, CA

Abstract: Humans can remember specific events without acting on them and can influence which memories are retrieved based on internal goals. However, current animal models of memory typically present sensory cues to trigger retrieval and assess retrieval based on action. As a result, it is difficult to determine whether measured patterns of neural activity relate to the cue(s), the retrieved memory, or the behavior. We therefore asked whether we could develop a paradigm to isolate retrieval-related neural activity in animals without retrieval cues or the requirement of a behavioral report. To do this, we focused on hippocampal “place cells.” These cells primarily emit spiking patterns that represent the animal’s current location (local representations), but they can also generate representations of previously visited locations distant from the animal’s current location (remote representations). It is not known whether animals can deliberately engage specific remote representations, and if so, whether this engagement would occur during specific brain states. So, we used a closed-loop neurofeedback system to reward expression of remote representations that corresponded to uncued, experimenter-selected

locations, and found that rats could increase the prevalence of these specific remote representations over time; thus, demonstrating memory retrieval modulated by internal goals in an animal model. Our neurofeedback system performed real-time spatial decoding using all hippocampal CA1 spikes above an amplitude threshold. This approach provides more accurate decoding than using only spikes that can be confidently associated with single neurons, but limits the conclusions that can be reached regarding single neuron activity. As memory retrieval is thought to engage the coordinated activity of ensembles of neurons, we also performed spike sorting and used the resulting putative single neuron data for cell assembly identification. We found assemblies that represented the specific target location and that the activity of these assemblies was enriched during times of remote representation. These results demonstrate engagement of coordinated ensembles of single neurons during remote spatial representations. These remote representations occurred predominately during periods of immobility but outside of hippocampal sharp-wave ripple (SWR) events. Representations outside of SWRs increased consistently with neurofeedback while representations within SWRs did not consistently increase. In summary, this experimental approach enables future direct studies of memory retrieval mechanisms in the healthy brain and in models of neurological disorders.

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Poster

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NIA Grant R01AG055544

Title: Unveiling the dynamics of hippocampal theta wave propagation in freely moving rats

Authors: *S. D. LOVETT[1], J. P. KENNEDY[1,2], Y. QIN[1,2], B. ZHAO[1,2], C. BESOSA[1,2], S. N. BURKE[1,2,3], A. P. MAURER[1,2,3,4,5];
[1]Neurosci., Univ. of Florida, Gainesville, FL; [2]Evelyn F. McKnight Brain Inst., Gainesville, FL; [3]Ctr. for Cognitive Aging and Memory, Gainesville, FL; [4]Dept. of Biomed. Engin., Gainesville, FL; [5]Engin. Sch. of Sustainable Infrastructure and Envrn., Gainesville, FL

Abstract: Understanding the mechanisms by which theta waves propagate across the hippocampus is of utmost importance in understanding various aspects of cognition in rodent models. A current hypothesis in the field is that hippocampal rhythms are synchronous throughout the medial temporal lobe. However, recent studies have concluded that theta oscillations travel as non-synchronous waves along the septotemporal axis of the hippocampus.

Our experimental goal was to derive a relationship between theta oscillations in the anterior and posterior regions of the hippocampus by examining local field potential in freely moving rats. We trained a mixed-sex cohort of five Fisher Brown Norway hybrid rats to run on a circular track for a food reward and implanted them with an intracranial silicon probe in the CA1 region of the anterior dorsal hippocampus (AP: -2.8 ML: 1.5 DV: 4.0) and the CA1 region of the posterior parietal hippocampus (AP: -5.6 ML: 4.2 DV: 4.5). After a recovery period, the rats were reintroduced to the circular track where data was collected from each site. We found that theta power increased as a function of velocity in the dorsal and ventral regions of the hippocampus. Additionally, a phase offset was observed between the raw LFP of the dorsal and ventral hippocampus, and the magnitude of this offset decreases as running speed increases. These findings suggest that theta may propagate across the hippocampus of rats in a traveling, non-synchronous manner with a phase offset dependent on running velocity.

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Poster

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R01 MH104602

Title: Hippocampal circuits for episodic social memory

Authors: D. GILLY SUAREZ[1], S. A. SIEGELBAUM[2], *P. KASSRAIAN[3];
[1]Columbia Univ., New York City, NY, ; [2]Dept of Neurosci., 5Department of Pharmacology, Vagelos Col. of Physicians and Surgeons, Columbia Univ. Irving Med. Center, New York, NY 10032, New York, NY; [3]Zuckerman Mind Brain Behavior Institute, Columbia University, New York, NY 10027 USA, 10024 New York, NY

Abstract: Prior work has demonstrated that the hippocampal cornu ammonis 2 (CA2) region is critical for social novelty recognition memory (SNRM) but not for canonical hippocampus-dependent spatial and contextual memory, raising the possibility of cortico-hippocampal circuits specialized for social information processing. Yet in contrast to canonical work demonstrating e.g., the transformation of spatial information into a place cell code throughout the cortico-hippocampal circuit, little is known about the mechanisms and computations which enable the processing of social information throughout these pathways. Here we investigate the role of CA2 upstream and downstream regions and of CA2 itself as a central hub for the processing of social information. By using a fear conditioning paradigm that has both social and spatial components (social/spatial fear conditioning or SFC), we expand beyond the study of SNRM and investigate

social episodic memories including the recollection of the valence or spatial location required to inform an animal's decision to approach or avoid a conspecific.Among other results, we find that CA1 pyramidal neurons (PNs) are required for discrimination of a threat-associated spatial location but are not necessary to discriminate a threat-associated conspecific (CS+) from a safety-associated conspecific (CS-). In contrast, CA2 PNs are not required to discriminate spatial location of a threat but are required for social threat discrimination. Thus, the targeted silencing of CA2 PNs results in generalized avoidance fear behavior towards the CS- and CS+ mice. One-photon calcium imaging from CA2 reveals that SFC modified the CA2 social representations of the CS+ and CS- in a manner that enhanced the ability of CA2 activity to discriminate the two individuals and led to the incorporation of a generalized or abstract representation of social valence into social identity representations. These results indicate that spatial and social threat discrimination are carried out independently by CA1 and CA2, respectively. Moreover, our findings show that CA2 not only discriminates a novel from familiar animal but also encodes valence associated with a social experience, demonstrating that social familiarity and recollection of a social episodic memory are encoded in the same brain region.

Disclosures: D. Gilly Suarez: None. **S.A. Siegelbaum:** None. **P. Kassraian:** None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.20/P10

Topic: H.09. Spatial Navigation

Support: NICHD Intramural Grant
NIH Center on Compulsive Behavior Fellowship
NICHD Early Career Award

Title: Selectivity and evolutionary conservation of inhibition in a pattern separation circuit

Authors: *G. VARGISH[1], X. YUAN[2], K. A. PELKEY[3], C. J. MCBAIN[4];
[1]NICHD, Bethesda, MD; [2]NIH, Bethesda, MD; [3]NICHD/LCSN, NIH, Silver Spring, MD; [4]Lab. Cell/Molec Neurosci, NIH, Bethesda, MD

Abstract: The mammalian dentate gyrus (DG) is widely implicated in pattern separation, a computation that distinguishes perceptually similar events by segregating overlapping inputs into discrete output patterns. While granule cells (GCs), the main excitatory cell type in the DG, were historically believed to drive pattern separation with their sparse activity profile and large cell numbers, recent evidence indicates that mossy cells (MCs), the other DG excitatory cell type, may play a critical role. In contrast to GCs, MCs are highly active and strongly innervate inhibitory interneurons (INs) in the DG. These divergent activity patterns coupled with MCs innervation of DG INs suggests that MCs drive disynaptic inhibition to actively shape GC sparseness, enabling pattern separation. The circuit-level mechanisms that generate and maintain

this high MC/low GC activity dynamic, though, remain poorly understood. Using a combination of optogenetics, electrophysiology and *in vivo* 2-photon Ca^{2+} imaging we found that selective inhibitory innervation patterns in the DG contribute to these circuit dynamics. In mice, we identified a novel subpopulation of DG INs, characterized by expression of vesicular glutamate transporter 3 (VGluT3), as the predominant source of inhibition onto MCs and showed that these VGluT3+ INs preferentially innervate MCs over GCs while parvalbumin(PV)-, somatostatin(SOM)- and VIP-expressing IN subgroups are biased towards GC innervation. 2-photon Ca^{2+} imaging in awake, behaving mice corroborated these findings showing that chemogenetic activation of VGluT3+ INs significantly reduced *in vivo* MC activity but not GC activity. Interestingly, electrophysiological recordings from non-human primate (NHP) and human tissue indicated that these patterns of inhibitory connectivity are evolutionarily conserved. Leveraging the prominent cannabinoid receptor expression in VGluT3+ IN axon terminals to probe VGluT3+ innervation patterns in NHP and human tissue, we found that inhibitory inputs onto MCs exhibited significantly more cannabinoid sensitivity when compared to GCs, consistent with dominant VGluT3+ IN innervation of MCs in these species. In addition, using novel enhancer viruses that selectively target PV+ and SOM+ INs we determined that PV and SOM selectivity for GCs over MCs is conserved in NHPs. These findings not only establish that MCs and GCs have unique, evolutionarily conserved IN innervation patterns but also suggest that selective inhibitory circuits may play a critical role in governing DG circuit dynamics and pattern separation across species.

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Poster

PSTR045: Intrinsic Hippocampal Circuits

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.21/P11

Topic: H.09. Spatial Navigation

Title: Insights into elite soccer player's brain: Hippocampal Tail volume correlates with cognitive performance

Authors: *A. QUDDUS[1], S. MAHARJAN[2], M. AL AMIN[3];
[1]Natl. Univ. Bangladesh, Gazipur, Bangladesh; [2]Brain Hlth. Imaging Institute, Weill Cornell Med., New York, NY; [3]Med. and Mol. Genet., Stark Neurosciences Res. Inst., Indianapolis, IN

Abstract: Success in soccer relies on complex motor skills and spatial awareness, such as positioning on the field, anticipating opponents' movements, and executing precise passes. The hippocampus plays a key role in encoding, consolidating, and retrieving spatial memories, which are essential for learning and adapting to the dynamic nature of the game. Studying hippocampal subfield volumes in soccer players would provide valuable insights into the cognitive, and neurobiological aspects of athletic performance. However, no such studies have investigated the effect of soccer training on hippocampal subfield volumes. We investigated the impact of soccer

training on hippocampal subfield volumes in professional soccer players. We analyzed a cohort comprising 25 soccer players (age, *mean* = 20.2, *sd* = 1.0) and 25 age-matched healthy controls (age, *mean* = 21.76, *sd* = 1.4). The mean experience of soccer players was 11.3 ± 1.95 years. T_1-weighted (TR =2900 ms; TE = 7.6 ms; matrix size 224 x 224; flip angle = 12°; slice thickness = 1 mm) magnetic resonance images (MRI) were analyzed to quantify hippocampal subfield volumes. Motion and biasfield corrected images were parcellated in freesurfer. Freesurfer's hippocampal subfield script was used to segment the hippocampal tail, subiculum, fissure, CA1, ML, GC-ML-DG, CA3, CA4, Fimbria, and HATA. There was a significant difference in the total intracranial volume (eTIV) between soccer players and healthy controls. Therefore, we normalized the volumes of the entire hippocampus and each hippocampal subfield using eTIV data. There was no significant difference in total hippocampal volumes. However, there was a trend toward higher right hippocampal volume in soccer players than in healthy controls. In addition, no statistically significant differences were observed in the volumes of the CA1, CA3, CA4, Molecular Layer, Dentate gyrus, Fimbria, and HATA subfields between soccer players and healthy controls. Interestingly, we identified significantly higher volumes of the hippocampal tail and fissure in soccer players. Furthermore, there was a significant correlation ($r = 0.61$, $p < 0.001$) between cognitive score and hippocampal tail volume in soccer players. We suggest that the hippocampal tail may have a critical role in soccer skills to efficiently navigate the game. Although the exact function of the hippocampal tail is not as extensively studied, further investigations incorporating longitudinal studies may provide deeper understandings into the relationship between soccer and hippocampal morphology.

Disclosures: A. Quddus: None. **S. Maharjan:** None. **M. Al Amin:** None.

Poster

PSTR046: Spatial and Nonspatial Coding in Hippocampal Neurons

Location: MCP Hall A

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Program #/Poster #: PSTR046.01/P12

Topic: H.09. Spatial Navigation

Support: NIMH Grant F32MH135680
NIMH Grant R01MH132204

Title: Dynamic coordination of spatial representations in hippocampus and anterior cingulate cortex ensemble activity during cognitive control

Authors: *G. J. BLAIR[1], A. A. FENTON[2];
[1]Ctr. for Neural Sci., NYU, New York, NY; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: We aim to understand how information is dynamically represented and coordinated across distinct brain regions. Navigating our daily lives requires the judicious use of limited cognitive resources to yield preferred outcomes, called cognitive control, which is known in

humans and animals to depend on the prefrontal cortex (PFC), including the anterior cingulate cortex (ACC). Our studies of rats and mice performing an active place avoidance task have also demonstrated the importance of hippocampus (HPC) for cognitive control. We performed single-photon miniscope calcium imaging in the ACC and HPC of freely-behaving rats to determine if a cognitive control signal is expressed in PFC ensemble activity and whether it is coordinated with HPC activity. Rats were transfected with AAV9-CaMKIIa-GCaMP8m in HPC dorsal CA1 and ACC, then gradient refractive index lenses were implanted above the injection sites. Rats were trained in the active place avoidance task on a rotating arena that can deliver a mild 0.2 mA shock in a 60° sector of the stationary room frame. Rotation requires rats to judiciously localize themselves and locations of shock within two conflicting reference frames at any time (the local rotating *arena* frame or the stationary *room* frame defined by distal cues). Because room and arena cues continuously change their relationships, avoiding shock requires cognitive control to utilize the appropriate cues that predict the location of the shock zone and is known to depend on hippocampus. Separate ensemble recordings of ACC and of CA1 demonstrate that cells in both regions are significantly modulated by position, though CA1 activity is more location-specific (greater mutual information per calcium event). Analysis of the momentary positional information (I_{pos}) time series computed from simultaneously recorded CA1 and ACC ensembles revealed a highly correlated spatial frame-specific representation of current location that purposefully alternates between the arena and room frames signaling cognitive control. Surprisingly, this signal is stronger in all ACC recordings compared to CA1. Decoding position using a Naïve Bayesian approach demonstrates the dynamic coordination of the two regions; they can alternate between representing approximately the same or very different locations of the room. This *bona fide* cognitive control signal in rodent PFC in coordination with CA1 demonstrates a paradigm to investigate mechanisms of how two distinct brain circuits coordinate neural population activity during cognitive control of spatial information processing and memory.

Disclosures: G.J. Blair: None. **A.A. Fenton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioSignal Group.

Poster

PSTR046: Spatial and Nonspatial Coding in Hippocampal Neurons

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.02/Q1

Topic: H.09. Spatial Navigation

Support: R01MH132204

Title: Interpreting the results of causal optogenetic manipulations

Authors: *C. GARCIA JOU[1], S. CARRILLO SEGURA[2], E. PARK[3], A. A. FENTON[3];
[1]City Univ. of New York, Brooklyn, NY; [2]Ctr. for Neural Sci., NYU Ctr. For Neural Sci., New York, NY; [3]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Optogenetics has revolutionized our understanding of memory formation, storage, and retrieval by enabling the precise manipulation of a subset of neurons active during encoding. Stimulating these “engram” cells induces the expression of a conditioned behavior. However precise, optogenetics is still the manipulation of a complex system with adaptive, non-linear, and homeostatic interactions. Therefore, interpreting the results of these experiments as a result of a causal manipulation has been challenging, since the network response to the optostimulation is unknown. Here, to assess the changes in single-cell and network dynamics to the optostimulation as a function of ongoing brain activity, we use the engram tagging approach and record from CA1 ensembles of Arc-CreERT2-ChR2 mice with optostimulation during anesthesia, head fixation, and foraging in a 2m track. Optostimulation of active place avoidance memory-tagged CA1 neurons activates ~14% of cells with sub-second latency. Under anesthesia, we observe an increase in activity and network synchronization to the light stimulation. During head fixation, cells that initially display short latency to light pulses progressively lose their response. During stimulation with 15-ms light pulses at 4Hz or 10Hz for 10min the network rapidly adapts with cells increasing, decreasing, or maintaining their baseline activity; the network also maintains cofiring relationships and thus the low-dimensional manifold organization of the population dynamics. During foraging, “place cells" were identified using coherence and place information criteria. Comparing pairs of unstimulated to baseline and optostimulated recording pairs, 43% vs. 48% of cells remained place cells, and a few gained a firing field (6.7% vs 7.5%). Population vector activity at each position was highly correlated between baseline and optostimulation ($r = 0.7$), indicating preserved network dynamics. This network resistance to change under optogenetic stimulation correctly predicted that the stimulation is sufficient to elicit the conditioned active place avoidance memory in a neutral environment. We conclude that optogenetic manipulations of memory-tagged cells are better interpreted as eliciting the endogenous population dynamics of a complex system, rather than the causal demonstration of neural circuit function.

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Poster

PSTR046: Spatial and Nonspatial Coding in Hippocampal Neurons

Location: MCP Hall A

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Program #/Poster #: PSTR046.03/Q2

Topic: H.09. Spatial Navigation

Support: R01MH132204
R01MH115304

Title: Hiding in plain sight: Place, context, taste and ambient sound in the conjoint activity of CA1 ensembles

Authors: S. CARRILLO SEGURA, E. R. LEVY, ***A. FENTON**;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Averaging the location-specific activity of single hippocampal neurons identifies a minority of hippocampal cells that discharge robustly in locations called "place fields," but we have argued such analyses of single neurons can mislead by explicitly ignoring cofiring amongst cells. Cofiring patterns define an information-rich, time-evolving manifold population code that cannot be observed by firing field-based analyses. We test this "cofiring" hypothesis by infecting dorsal CA1 with AAV-GCaMP6f and using UCLA miniscopes to record CA1 ensemble activity in separate spatial and non-spatial experiments, each characterized by multiple classes of distinct yet simultaneously useful information. The spatial experiment used a 1-rpm rotating disk with a parallel-rod floor. Mice (n = 5) explored freely in the "*neutral*" condition with a clear plastic film on the floor and they avoided a stationary shock zone without the plastic in the "*avoidance*" condition. The cofiring hypothesis predicts that despite indifferent place fields, conjoint ensemble activity distinguishes the *neutral* and *avoidance* conditions. The non-spatial experiment also used a single environment, a cage in which mice consume their daily ration of water during the third of five 7-min epochs (*silent, sound, sound+water, sound, silent*). Once familiar, changing the water's taste reduces consumption that attenuates the next day (attenuation of taste neophobia - ATN), but not if the ambient sound also changes the next day; this disruption of ATN depends on hippocampus. The cofiring hypothesis predicts that despite indifferent place fields, conjoint ensemble activity will distinguish the non-spatial contexts. The prevalence, quality and stability of place fields was unchanged across the *neutral* and *avoidance* conditions, and unchanged across the ATN experiment. CEBRA, a non-linear machine learning algorithm identified latent subspaces defined by conjoint neuronal population activity that reliably encode position, spatial frame (stationary or rotating), and the distinct *neutral* and *avoidance* contexts. Stability of the latent subspaces encoding the *neutral* and *avoidance* contexts increased with experience. Similarly, latent subspaces defined by cofiring during the ATN experiment reliably encoded the taste and sound contexts. These findings support the cofiring hypothesis and demonstrate its utility by decoding the positional information in the conjoint discharge of CA1 neurons and by revealing extra-positional information about spatial and non-spatial context, which is undetected by analyses that rely on single-neuron tuning properties that ignore their cofiring.

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Poster

PSTR046: Spatial and Nonspatial Coding in Hippocampal Neurons

Location: MCP Hall A

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Program #/Poster #: PSTR046.04/Q3

Topic: H.09. Spatial Navigation

Support: NIH Grant MH125655
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NIH Grant MN131317

Title: Assessment of abnormalities in hippocampal replay events in a rat model of Fragile X Syndrome

Authors: *M. M. DONAHUE[1,2], E. ROBSON[1,3], L. L. COLGIN[1,2,3];
[1]Ctr. for Learning and Memory, Univ. of Texas at Austin, Austin, TX; [2]Institute for Neuroscience, University of Texas at Austin, Austin, TX; [3]Department of Neuroscience, University of Texas at Austin, Austin, TX

Abstract: Fragile X Syndrome (FXS) is a neurodevelopmental disorder that can cause impairments in spatial cognition. The hippocampus is thought to support spatial cognitive functions through the activity of place cells, neurons with spatial receptive fields. The reactivation or "replay" of previously active place cell sequences during sharp wave-ripples (SWRs) is believed to be important for spatial memory-guided planning and spatial memory consolidation. Previous research has shown that SWRs are abnormal in a mouse model of FXS (Boone et al. 2018), but to our knowledge the replay of place cell sequences during SWRs has not been examined in a rodent model of FXS. Here, we examined whether SWR-associated replay was impaired in a rat model of FXS (*Fmr1* knock-out rats or "FXS rats"). We recorded CA1 place cell populations in 4 FXS rats and 4 wild-type (WT) control rats during unidirectional running on a circular track and subsequent waking rest periods. We then used a Bayesian decoding algorithm to estimate angular positions on the circle track represented by populations of CA1 place cells during replay events. Our preliminary results suggest that replay fidelity was similar between WT and FXS rats. However, replay events were longer in duration in FXS rats. Further, the temporal compression of sequences of locations represented during replay events was lower in FXS rats. These results raise the possibility that impairments in SWR-associated replay contribute to aberrant spatial cognitive functions in FXS.

Disclosures: M.M. Donahue: None. **E. Robson:** None. **L.L. Colgin:** None.

Poster

PSTR046: Spatial and Nonspatial Coding in Hippocampal Neurons

Location: MCP Hall A

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Program #/Poster #: PSTR046.05/Q4

Topic: H.09. Spatial Navigation

Support: NIH Grant MH125655
NIH Grant MH127933
NIH Grant MN131317

Title: Deciphering deficits in CA2 place cells in a rat model of Fragile X syndrome

Authors: *E. J. FERNANDEZ, E. ROBSON, M. DONAHUE, L. L. COLGIN;
Ctr. for Learning and Memory, Univ. of Texas at Austin, Austin, TX

Abstract: Hippocampal area CA2 is essential for social memory. CA2 contains spatially modulated "place cells" that change their firing patterns ("remap") during social interactions (Alexander *et al*., 2016). Our unpublished data has shown that exposure to a social odor is sufficient to cause remapping in CA2 place cells (Robson et al., Society for Neuroscience 2023 Abstracts). Fragile X Syndrome (FXS) is a neurodevelopmental disorder associated with abnormal social behaviors. Preliminary data suggests that CA2 place cell responses to social odors may be impaired in a rat model of FXS (*Fmr1* knockout rats or "FXS rats"). FXS is caused by the absence of the Fragile X Messenger Ribonucleoprotein (FMRP) in neurons. FMRP is widely expressed in the brain, including in olfactory regions. To determine if abnormal CA2 place cell remapping is due to impaired olfaction in FXS rats, we assessed the functionality of the olfactory system in FXS rats (n = 12) and wildtype (WT) control rats (n = 12) using an olfactory habituation/dishabituation test. Results indicate that FXS rats have intact olfactory perception and can distinguish between different social and non-social odors. Activity of CA2 neurons can be modulated oxytocin, a neuropeptide that has been associated with social behaviors. This raises the possibility that impaired CA2 place cell remapping may result from reduced expression of oxytocin receptors in CA2 of FXS rats. We immunostained brain slices from FXS (n = 2) and WT (n = 2) rats with an oxytocin receptor antibody and a marker for CA2, Purkinje cell protein 4 (PCP4). Robust oxytocin receptor expression was observed in CA2 of both FXS and WT rats. These preliminary results suggest that impaired CA2 place cell responses to social odors are not due to olfactory dysfunction or a lack of oxytocin receptors in CA2.

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Poster

PSTR046: Spatial and Nonspatial Coding in Hippocampal Neurons

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Topic: H.09. Spatial Navigation

Support: NIH Grant MH125655
NIH Grant MH127933
NIH Grant MN131317

Title: Are CA2 place cell responses to social stimuli impaired in a rat model of Fragile X Syndrome?

Authors: *E. ROBSON, M. M. DONAHUE, A. J. MABLY, P. G. DEMETROVICH, L. T. HEWITT, L. L. COLGIN;
Ctr. for learning and memory, Univ. of Texas at Austin, Austin, TX

Abstract: The CA2 subregion of the hippocampus has been implicated in social memory. CA2 contains “place cells”, neurons with spatial receptive fields (“place fields”). Our previously published work in wildtype (WT) rats showed significant place field changes (“remapping”) in CA2 during exploration of an open-field environment in which a conspecific rat was presented in its homecage (Alexander et al., 2016). Our new unpublished results show that presentation of social odors alone can also induce CA2 place cell remapping. Fragile X Syndrome (FXS) is a neurodevelopmental disorder associated with abnormal social behaviors and impaired processing of sensory stimuli. Therefore, it is possible that CA2 place cells show abnormal responses to social stimuli in FXS. In the present study, we recorded CA2 place cells in WT control rats (n=6) and in a rat model of FXS (Fmr1 knockout rats or “FXS rats”) (n=4) as social odors were presented in an open-field arena. Preliminary results suggest that CA2 place cell remapping to social odors is impaired in FXS rats. Furthermore, prior work showed that CA2 place cells that fire during social exploration of novel conspecifics reactivate in sharp-wave ripples (SWRs) during subsequent rest (Oliva et al., 2020). Therefore, we analyzed CA2 place cell firing in SWRs of FXS rats and WT rats during rest periods following exploration of an arena containing familiar social odors. Preliminary results suggest that CA2 place cells that preferentially fired in response to social odors strongly increased their firing rates during subsequent SWRs in WT, but not FXS, rats. These results suggest that impaired CA2 place cell coding of social stimuli may contribute to deficits in processing of social stimuli in FXS.

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Poster

PSTR046: Spatial and Nonspatial Coding in Hippocampal Neurons

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Program #/Poster #: PSTR046.07/Q6

Topic: H.08. Learning and Memory

Support: National Science Foundation Graduate Research Fellowship under Grant No. DGE-2241144
NIH grant MH116267

Title: Calcium Activity Patterns of Mouse Dorsal CA1 Hippocampal Neurons During Object Exploration

Authors: *S. GAVADE[1], S. YANG[2], J. L. SPENCER-SEGAL[3];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Univ. of Michigan Neurosci. Grad. Program, Univ. of Michigan, Ann Arbor, MI; [3]Michigan Neurosci. Inst., Univ. of Mchigan, Ann Arbor, MI

Abstract: Object recognition is an important test used to study memory processes in laboratory rodents. Prior work has shown that the dorsal CA1 of the hippocampus in rodents is important for object recognition. Yet, very little is known about how dorsal CA1 neurons encode the

attributes of objects, such as object identity and novelty, that are important for this task. To study this, we recorded calcium activity in CA1 pyramidal neurons using a miniature microscope in a freely moving mouse interacting with familiar or novel objects over several days in the same, familiar arena. Three different objects were used with multiple presentations. We identified an average number of 408 neurons per recording session; 160 individual neurons could be followed across all trials. Dorsal CA1 neurons exhibited increased synchrony of calcium activity (correlated activity) during object exploration. We identified distinct groups of neurons active during object exploration on individual days, "object cells," by comparing the observed activity to a shuffled data distribution. We found that on average, 21.32% of neurons were object cells. The specific neurons in the object cell population changed considerably across days regardless of object identity or familiarity. To further analyze these findings, we implemented a neural decoder using a supervised learning model SVM (Support Vector Machine) classifier. This approach allowed us to decode the neural activities associated with exploratory behavior, including the classification of object identity. In addition, we applied UMAP (Uniform Manifold Approximation and Projection) for dimensionality reduction, which facilitated the identification of distinct neural activity clusters related to the familiarity and novelty of objects. These techniques combined provide a robust framework for understanding the neural signature of object recognition in dorsal CA1 neurons.

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Poster

PSTR046: Spatial and Nonspatial Coding in Hippocampal Neurons

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Topic: H.09. Spatial Navigation

Support: STI2030-Major Projects (Brain Project in China)Ministry of Science and Technology of the People´s Republic of China (2021ZD0203600)
NSFC (32271088)

Title: Neural representations of space and time in the hippocampal CA3 and dentate gyrus of behaving common marmosets

Authors: *F. QIAO[1,2], L. GAO[3], Y. SAKURAI[5], A. NAMBU[6], A. W. ROE[4], **Y. NAYA**[2,7];
[1]PKU, Beijing, China; [2]Peking Univ., Sch. of Psychological and Cognitive Sci., Beijing, China; [3]Interdisciplinary Inst. of Neurosci. and Technol. (ZIINT), [4]Interdisciplinary Inst. of Neurosci. & Technol., Zhejiang Univ., Hangzhou, China; [5]Grad. Sch. of Brain Science, Doshisha Univ., Kyotanabe-Shi, Japan; [6]Div. Syst. Neurophysiol, Natl. Inst. Physiol Sci., Okazaki, Japan; [7]Peking Univ., PKU-IDG/McGovern Inst. for Brain Res., Beijing, China

Abstract: Numerous studies investigated neural representations of space and time using rodents and identified place cells and time cells in the hippocampus. However, only few studies have

explored them using nonhuman primates. To investigate how space and time are processed in the primate brain, we recorded hippocampal neuronal activity in freely moving common marmosets. We trained two common marmosets to travel three small platforms (10 cm, diameter) sequentially according to a flash of LED light under the platforms in an open-field rectangular arena (2.0 m × 1.5 m) ("sequential look and go task"). Microwire brush array electrodes (16 channels) were implanted in the hippocampus, and neuronal signals were wirelessly transmitted. We recorded neuronal activity of 421 neurons in the CA3 region and 349 neurons in the dentate gyrus (DG) of the two animals during the task. Substantial number of neurons in the CA3 (47.3%) and ventral layer of DG (vDG) (48.7%) showed significantly ($p < 0.01$) selective responses when the animals stayed at particular locations ("place cells"). In contrast, there were only a few place cells (2%) in the dorsal layer of DG. We examined a temporal-order effect on the space-selective responses and found that a larger proportion of place cells showed a significant ($p < 0.05$) temporal-order effect to represent a particular place ("where") at a particular temporal order ("when") in the CA3 than vDG (43.8% > 10.4%, $p < 0.01$, $\chi^2=16$). These results suggest an existence of substantial number of place cells in the primate hippocampus and an increase of the temporal-order effect along the anatomical hierarchy from the DG to CA3.

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Poster

PSTR046: Spatial and Nonspatial Coding in Hippocampal Neurons

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Topic: H.09. Spatial Navigation

Support: R01-MH104606

Title: Representations of spatial and reward structure in human hippocampal neurons

Authors: *W. ZHANG[1], S. MAESTA PEREIRA[1], T. DONOGHUE[1], O. ARAIZA CARRANZA[2], B. C. LEGA[3], I. SAEZ[4], J. JACOBS[5];
[1]Biomed. Engin., Columbia Univ., New York, NY; [2]UT Southwestern Med. Ctr., Dallas, TX; [3]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX; [4]Mount Sinai, New York, NY; [5]Dept. of Biomed. Engin., Columbia Univ., New York, NY

Abstract: Spatial navigation is a complex cognitive process through which humans and animals navigate and select optimal routes toward goals to maximize long-term rewards. Prior research suggests that the hippocampal-entorhinal system is pivotal in this cognitive process by constructing a geometric representation of space, with hippocampal place cells activating in specific locations. However, it is unclear how additional elements, such as reward structure, are integrated. One framework that addresses this limitation is the Successor Representation (SR)

model. SR model features a predictive map for caching long-term state occupancy and a reward function for encoding immediate rewards, supporting a dynamic, general-purpose map that integrates and updates spatial and reward information to optimize navigational choices. In this study, we investigate the role of the human hippocampus in goal-directed navigation, specifically in the context of SR-based models. We hypothesize that the firing patterns of hippocampal place cells mirror features of the SR predictive map, and the activity of reward-associated cells reflects the SR reward function. Collectively, the human hippocampal neurons support an SR-based general-purpose map. Our analysis uses single-unit recordings from patients with drug-resistant epilepsy engaged in a virtual reality task - "SpaceHeist," participants navigate two parallel paths of rooms to discern which leads to greater monetary rewards. The task involves the initial learning phase and subsequent adaptation phase - where reward amounts or room sequences change, necessitating a precise relational representation of the spatial environment and its associated rewards. Utilizing the SR algorithm, we simulated human behavior and the firing patterns of place and reward-associated cells under respective task conditions. Participants showed high accuracy in responding to both reward and spatial questions in both phases, suggesting that they learned and updated their cognitive map in response to the task. Moreover, shorter response times for reward questions highlight a higher cognitive sensitivity to reward-related information, aligning with the SR model's prediction. We then examined the computational functions of hippocampal place cells. Here, we observed a potential directional bias in the form of backward expansion in human place cells, which appears to align with the SR model's prediction of a predictive skewing feature. Though this tendency hints that place cells may prioritize goal-oriented spatial information, further investigation is needed to establish that neurons in the human hippocampus construct a general-purpose map.

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Poster

PSTR046: Spatial and Nonspatial Coding in Hippocampal Neurons

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.10/R3

Topic: H.08. Learning and Memory

Title: Investigating human single unit responses to word concepts in the Mesial Temporal Lobe

Authors: *L. SARMIENTO[1], J. S. GARCIA SALINAS[2], S. PRATHAPAGIRI[1], J. KAMINSKI[3], M. MAGNUSKI[4], M. T. KUCEWICZ[2];
[2]Multimedia Systems, [1]Gdansk Univ. of Technol., Gdansk, Poland; [3]Neurosurg., The Nencki Inst. of Exptl. Biol., Warsaw, Poland; [4]Nencki Inst. of Exptl. Biol., Warsaw, Poland

Abstract: Investigating human single unit firing responses to word concepts in the Mesial Temporal Lobe Luis Felipe Sarmiento, Jesus Garcia Salinas, Sathwik Prathapagiri, Mikolaj Magnuski, Wojciech Fortuna, Monika Sluzewska, Pawel Tabakow, Jan Kaminski, Michal

Kucewicz

Single unit recording is instrumental in deciphering the intricate activity patterns of individual neurons in the human brain, offering insights into cognitive functions. In this study, we aimed to elucidate the firing responses of specific neurons in the human hippocampus and the associated mesial temporal cortex to specific words. Five patients with depth micro-electrode wires implanted in the temporal cortex participated in this study during intracranial EEG monitoring for treatment of drug-resistant seizures. Over the course of three days, each patient underwent a series of cognitive tasks, including Free Recall (FR), Pair-Associated Learning (PAL), and Word Screening (WS). During the WS task, patients were instructed to recall the last word presented before seeing question marks on pseudorandomly assigned trials. Each trial involved presenting one of 180 different words in a block with each block repeated five times in one session (900 word presentations in total). The task allowed for identification of statistically significant responses to particular words. Extracellular action potentials, aka spikes, were isolated into individual single unit activities (SUA) over the entire recording session, including the FR, PAL and WS tasks. In total, 144 neurons were isolated across 13 sessions from the five patients with a max. of 36 units per session. We found significantly increased SUA rates in response to particular words presented across the three tasks. Our results suggest common neuronal mechanisms engaged in tasks probing different forms of memory and attention, supporting the view of SUA in the mesial temporal lobe as the building blocks of declarative memory.

Disclosures: L. Sarmiento: None. **J.S. Garcia Salinas:** None. **S. Prathapagiri:** None. **J. Kaminski:** None. **M. Magnuski:** None. **M.T. Kucewicz:** None.

Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.01/R4

Topic: H.10. Human Learning and Cognition

Title: Towards a lab-model of learned helplessness: The interplay between experimental heat pain and transcranial magnetic stimulation on reinforcement learning with manipulated outcome controllability

Authors: *G. CSIFCSÁK[1], S. BABIKER[1], F. LUZZI[2,3], M. MITTNER[4];
[1]Univ. of Tromsø, Tromsø, Norway; [2]Dept. of Neurosci. and Rehabil., Univ. of Ferrara, Ferrara, Italy; [3]Center for Translational Neurophysiology of Speech and Communication, Italian Institute of Technology, Ferrara, Italy; [4]Dept. of Psychology, Univ. of Tromsø, Tromso, Norway

Abstract: Repeated exposure to uncontrollable aversive events is associated with the state of learned helplessness (LH), characterized by passivity, weaker exploration tendencies and maladaptive coping. LH is prevalent in chronic pain syndromes, but it remains to be explored if experimental pain in the healthy can induce choice behavior resembling LH. Furthermore, while the medial prefrontal cortex (mPFC) has been linked to pain perception, estimations of

environmental controllability and cognitive processes underlying reinforcement learning (RL), the putative causal relationship between mPFC activity and LH-like behavior in the context of RL and pain is still unclear. This study addressed whether experimental heat pain (EHP) can shift healthy adults' decision-making strategies in a way that is consistent with LH (i.e., impaired post-EHP performance, inaction, reduced exploration). Moreover, we tested if EHP enhances Pavlovian response tendencies, which would be consistent with recent work pointing at a link between LH and Pavlovian bias over instrumental choices. Finally, we applied non-invasive intermittent theta-burst stimulation (iTBS) above the mPFC to counteract the anticipated detrimental effects of EHP on performance. In line with a pre-registered protocol, 100 participants were randomized into 4 groups following a 2 x 2 design (EHP x iTBS). Participants performed 3 blocks of an orthogonalized Go/NoGo task intervened with 2 bouts of either real or sham iTBS. EHP or warm stimulation was delivered to the forearm during block 2, which also entailed a manipulation of outcome controllability. Analysis of response accuracy and reaction times (RT) was supplemented with computational modeling to estimate latent parameters of RL. Surprisingly, neither EHP nor iTBS interfered with accuracy or subjective ratings of control. However, RT analysis indicated faster responses in "Win" (but not in "Loss") trials following EHP, being suggestive of enhanced Pavlovian bias. Computational modeling revealed LH-like choice behavior both during and following EHP, with weaker exploration, learning rate and action bias. Interestingly, iTBS led to largely similar effects to EHP alone, except for the reduction of the Pavlovian parameter following 2 stimulation bouts. Crucially, this effect was absent when preceded by EHP, pointing at the expected antagonism between EHP and iTBS in shaping Pavlovian-instrumental interactions. Our study provides empirical evidence for the role of experimental pain and mPFC activity in adopting choice strategies resembling LH in healthy adults, and may have implications for understanding cognitive symptoms of chronic pain syndromes.

Disclosures: G. Csifcsák: None. **S. Babiker:** None. **F. Luzzi:** None. **M. Mittner:** None.

Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.02/R5

Topic: H.10. Human Learning and Cognition

Title: The effect of reward on existing neutral memory representations and consequences for decision-making

Authors: *S. LEE[1,2], A. BAKKOUR[1,2,3];
[1]Dept. of Psychology, [2]Inst. for Mind and Biol., [3]Neurosci. Inst., Univ. of Chicago, Chicago, IL

Abstract: The inclination to repeat decisions based on past rewarding experiences is an inflexible form of decision-making because it fails to adapt in novel situations where direct past experiences cannot guide decisions. Cognitive graphs, which are internal models that represent

relations between prior experiences, have been used to examine how flexible decisions are made. Studies have found that humans are able to learn complex graph structures, such as the community structure, remember them, and use them to make decisions involving inference and generalization. However, no study has investigated how reward might alter the existing memory representation of a neutral cognitive graph nor the impact of such alteration on decision-making. Prior research has found that reward spreads to unrewarded items in memory in a graded manner (i.e., items closer to reward are remembered better than items further from reward), but it is unclear how reward spreads across cognitive graphs. We hypothesized reward might spread to items in memory in a graded manner and the structure of knowledge formed and represented by a cognitive graph might affect the way reward spreads across memory associations. Participants took part in a study consisting of four phases: (1) graph learning, which required learning a 15-node/fractal community structure graph from a sequence of fractal pairs that are connected on the graph; (2) graph test, where participants reconstructed the graph by grouping and drawing lines between fractals; (3) reward learning, which required learning fractal-reward associations for two fractals from the graph and two novel ones paired with either reward or neutral outcome; and (4) decision-making, where participants chose which fractal was more likely to lead to potential monetary reward from a pair of fractals. Results (N=134) show that participants' choices were influenced by the proximity of the fractal to reward but the spread of reward throughout the community structure graph was not graded. Reward seemed to spread uniformly to fractals near reward (1 or 2 links away equally well) and not spread to fractals far from reward (3 links away). This non-graded sensitivity to distance from reward when making value-based decisions was observed in both participants who learned and those who did not learn the structure of the graph. The present study investigates how reward might change the associations between experiences in memory and in turn affect decision-making. Through this study, we can gain a better understanding of how adaptive decision-making functions and as an extension, how maladaptive decision-making might occur.

Disclosures: S. Lee: None. **A. Bakkour:** None.

Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.03/R6

Topic: H.10. Human Learning and Cognition

Title: Noise correlations in feature learning

Authors: *X. DAI[1], J. KIM[2], A. BHANDARI[3], M. R. NASSAR[4];
[1]Neurosci., Brown Univ., Providence, RI; [2]Brown Univ., Providence, RI; [3]Cognitive Linguistics and Psychological Sci., Brown Univ., Providence, RI; [4]Metcalf Hall, Brown Univ., Providence, RI

Abstract: In real-word learning, individuals continually encounter complex arrays of features, only some of which are crucial to the outcomes they experience. How do they manage to discern which combinations of features are relevant for learning? This study explores how dynamic noise correlations - contextually enhanced correlations in neuronal firing - can focus learning on the most relevant feature dimensions in the current context by leveraging prior experience with these features. Participants were tasked with discriminating multi-dimensional perceptual stimuli under various task conditions that specifically incentivized learning about distinct, combined feature dimensions. We identified some evidence, based on single trial learning gradients, that people learned preferentially in relevant feature dimensions, but to a degree that differed considerably across individuals. These results motivate ongoing work modeling human subject behavior with neural networks and probing noise correlations in feature representations with fMRI. Our approach provides a window into how adaptive neural mechanisms can enhance the efficiency of learning in complex environments.

Disclosures: **X. Dai:** None. **J. Kim:** None. **A. Bhandari:** None. **M.R. Nassar:** None.

Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

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Program #/Poster #: PSTR047.04/S1

Topic: H.10. Human Learning and Cognition

Support: NIH Grant R01 MH131532-01
Brain & Behavior Research Foundation NARSAD Grant 28187

Title: The effect of trauma exposure on location-specific reward learning and attention to rewarding vs contextual cues

Authors: *C. SHARP[1], C. MARINO[1], P. RJABTSENKOV[1], E. PINEDA[1], T. GARG[1], S. BAVDEKAR[1], K. JORDAN[1], M. HALVORSEN[1], C. APONTE[1], A. LAZAROV[2], B. SUAREZ-JIMENEZ[1];
[1]Univ. of Rochester, Rochester, NY; [2]Tel Aviv Univ., Tel Aviv, Israel

Abstract: Individuals with trauma-related psychopathology commonly experience a decreased pursuit and anticipation of reward. However, little is known regarding how trauma exposure affects one's ability to learn where they may receive a reward in their environment. The effect of trauma on attention allocation to conditioned reward cues also remains unclear. Here, we combine a virtual reality (VR) reward conditioning task with fMRI to examine the impact of trauma exposure on location-specific reward learning and use eye-tracking to examine attention allocation to rewarding vs contextual cues from the VR task. Trauma-exposed (TE) and trauma-naïve (TN) participants completed a reward conditioning task in non-immersive VR in which they were asked to collect asteroids that appeared one-by-one in a virtual moon crater. On one half of the environment, 50% of the asteroids were paired with a reward. For each asteroid,

participants rated their expectancy of receiving a reward. After the task, we asked them to identify the reward reinforcement pattern. We also recorded brain activity throughout the task using fMRI. Before and after the VR task, participants completed an eye-tracking task during which they freely viewed matrices of images of the conditioned reward cues (MN) and environmental context (CX) from the task. We compared participants' total dwell time and first fixation dwell time on each cue type as measures of attentional bias. Our preliminary results show that both TEs and TNs that learned the reinforcement contingencies reported higher expectancy of receiving a reward in the rewarding zone, compared to the non-rewarding zone, with no significant differences between groups. However, fewer TEs (45%) were able to identify the rewarding zone after the task compared to TNs (58%). While not statistically significant, first fixation dwell time on CX vs MN cues decreased from before to after the task in TEs, but not in TNs. We found no significant Group x Timepoint interaction in percent of total dwell time on CX cues compared to MN cues. The directionality of our preliminary findings suggests that trauma exposure may decrease individuals' ability to discriminate rewarding areas of an environment. This may be explained by an attentional bias toward conditioned reward cues in trauma exposed individuals.

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Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.05/S2

Topic: H.10. Human Learning and Cognition

Title: Diffusion Models to Uncover the Underlying Mechanisms of Decoded Neurofeedback

Authors: *H. AZIMI ASRARI[1], M. A. PETERS[2];
[1]Univ. of California, Irvine, Irvine, CA; [2]Cognitive Sci., UC Irvine, Irvine, CA

Abstract: Decoded Neurofeedback (DecNef) entails altering a participant's pattern of brain activity by providing real-time feedback through functional magnetic resonance imaging (fMRI). This process involves passing a participant's current brain state to a classifier that has been pre-trained on desired brain patterns, allowing for targeted adjustments in neural activity patterns rather than overall univariate response. However, DecNef's efficacy varies widely across neural targets and individuals, such that the mechanisms by which (some) humans can successfully modulate some patterns of brain activity - but not others - remain unknown.Here, we investigated the combined use of diffusion models and reinforcement learning to reveal the policies involved in transforming random neural states into a target pattern state, as occurs during successful DecNef studies. Specifically, we used a new methodology called Denoising Diffusion Policy Optimization (DDPO), which uses diffusion models enhanced by reinforcement learning, to

extract the brain state transition policy. The model employs a deep neural network, known as a policy network, which assigns a transition matrix as an action to each state, defined by the timestep and current brain state. We applied this approach to pre-existing fMRI datasets from the DecNef Collection database, optimizing our diffusion models to replicate specific neural activity patterns (voxel-based).Our models successfully learned to increase the total reward gained across learning trials, emulating successful human participants in achieving target patterns. This suggests that the models were able to adapt their policy effectively to meet predefined goals, reflecting a capacity for sophisticated learning and adaptation similar to that observed in human subjects. Our findings demonstrate the effectiveness of the DDPO approach in discovering policies that achieve predetermined brain states, providing a solid base for better understanding of neurofeedback mechanisms and their practical applications in enhancing neurofeedback experiments.

Disclosures: H. Azimi Asrari: None. **M.A. Peters:** None.

Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

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Topic: H.10. Human Learning and Cognition

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Title: Human reinforcement learning of reachable space

Authors: *T. ZHU[1], R. SYAN[1], D. M. WOLPERT[2], J. P. GALLIVAN[1], J. FLANAGAN[1];
[1]Queen's Univ., Kingston, ON, Canada; [2]Columbia Univ., New York, NY

Abstract: Reinforcement learning has been used to explain how people learn and represent large-scale environments for spatial navigation. However, it remains unclear how people learn and represent “reachable” space when performing manual tasks such as preparing drinks at a coffee bar. To study the mechanisms underlying the learning and representation of reachable space, we developed a haptic maze task—adapted from a recent study of spatial navigation (de Cothi et al., 2022)—in which, in each trial, our human participants reached to a target while learning to avoid invisible haptic obstacles in the environment. The environment was a 10 x 10 grid of cells (2 x 2 cm), with obstacles defined by contiguous cells. Participants reached with a robotic handle that provided realistic contact forces to simulate the maze boundary, obstacle walls, and the floor, which supported the hand. Participants could see the maze boundary but not the maze obstacles or their hand position (1 cm sphere). They received audio feedback upon successfully reaching the target, the position of which was shown at the start of the experiment

and fixed throughout. We tested participants on 25 unique mazes, performing 10 reach trials within each maze from varying starting positions. The hand was guided to the start position by the robot before each trial. We fit and compared the likelihoods of 3 different reinforcement learning models: model-based (MB), model-free (MF) and successor representation (SR). MB agents (simulated participants) learned a map of the maze and planned the shortest route to the target. MF agents cached and updated expected total future reward for each action and selected highest-reward actions. SR agents learned a predictive map between grids (states) and integrated it with the target location (reward) to select actions. For all 12 participants, MB learning was favoured over both SR and MF learning. For 7 participants, SR learning was favoured over MF learning whereas for the other 5 participants, MF learning was favoured over SR learning. We also simulated the models under each participant's best-fit parameters. In terms of success rate (proportion of trials in which the target was reached) and average reach path lengths, simulated behaviour of MB agents was closer to optimal and more similar to humans' in comparison to SR and MF agents. Our findings suggest that humans primarily rely on MB reinforcement learning to complete movement tasks in rapidly-changing reachable spaces.

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Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.07/S4

Topic: H.10. Human Learning and Cognition

Support: NIH T32 EB029365

Title: Characterizing high-order interactions during conflict processing in patients with epilepsy

Authors: *A. MERKLEY[1], A. K. FELDMAN[2], D. M. KUSYK[3], A. C. WHITING[4], P. GROVER[5];
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA; [3]Neurosurg., Allegheny Hlth. Network, Pittsburgh, PA; [4]Neurosurg., Allegheny Hlth. Network, Neurosci. Inst., Pittsburgh, PA; [5]Electrical & Computer Engin., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The Stroop word-color task is a classic paradigm in psychology to assess conflict processing in humans. In the task, participants are shown words of different colors (e.g., red, green, or blue) written in either the same font color as the word (congruent) or in a different font color (incongruent). They are then asked to report the font color, not the word, by selecting a key. Recent studies have demonstrated in both electroencephalography (EEG) and stereo-EEG (sEEG) that multiple brain regions are activated in response to incongruent stimuli relative to congruent stimuli. This suggests a network dedicated to processing convergent, but conflicting,

streams of information. In this work, we investigate the activation of this network using data we collected from four patients with epilepsy implanted with several sEEG depth electrodes. Based on previous literature in conflict processing in the Stroop task, we consider the cingulate cortex, gyrus rectus, amygdala, and hippocampus. We identify possible paths of information flow and pairwise influence between regions by computing the Granger causal influence between the aforementioned brain regions. However, pairwise measures of dependency, such as the correlative measure used in Granger causality, may be insufficient to fully characterize the joint neural activity in more than two regions. Such complex systems can be modeled by their overall redundancy and synergy, which are two measures that provide greater insight than pairwise dependency. Redundancy refers to the amount of information each region shares, while synergy refers to the information that is available in the whole system, but not present in any individual region. Using O-information, an information-theoretic measure of redundancy and synergy, we characterize high-order interactions of the brain regions activated during stimulus presentation and key selection. We find that O-information reveals a richer structure in the network than that revealed by pairwise Granger causality. Furthermore, the O-information analysis provides an alternative interpretation to Granger causality of the joint activity in the conflict processing network.

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Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

Location: MCP Hall A

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Program #/Poster #: PSTR047.08/S5

Topic: H.10. Human Learning and Cognition

Support: NSF CAREER Award BCS1943767

Title: Effects of Exogenous Attention on Reward Learning and Probabilistic Inference

Authors: *A. SHAHAMATI, J. LIM, S. PARK, A. SOLTANI;
Dartmouth Col., Hanover, NH

Abstract: In naturalistic settings where numerous cues may be predictive of reward outcomes, both internal and external information compete to direct attention. This competition is crucial in determining which cues are utilized for decision making and/or are given credits for subsequent reward outcomes (i.e., learning). Although numerous studies have demonstrated that endogenous attention can influence reinforcement learning by determining relevant features or task dimensions, the role of exogenous attention in reward learning, especially from multiple cues, remains poorly understood. In this study, we investigated the mechanisms by which exogenous attention impacts learning and decision making using a novel experimental paradigm combined with eye tracking and computational modeling. More specifically, in a modified weather-

prediction task in which participants used multiple visual cues (abstract shapes) to predict one of the two choice targets (Windy vs. Rainy), we manipulated exogenous attention by increasing the saliency of a certain cue while participants simultaneously learned about all cues through reward feedback. In addition, we asked participants to provide their estimates about the predictive power of individual shapes or combinations of shapes throughout the experiment. Using a logistic regression model to extract the influence of individual shapes on choice behavior over time, we observed that enhanced saliency of a particular shape (salient shape) initially impeded learning by causing an overestimation or underestimation of the predictive value of that shape, depending on whether the salient shape provided evidence in support of the more rewarding choice target. Participants' estimates about the predictive power of each shape (i.e., inference) exhibited the same biases. These effects, however, gradually decreased over time due to ongoing reward feedback. Additionally, using the pattern of eye movements, we found that in the absence of saliency manipulation, attention was directed to shapes that were most predictive of the more rewarding choice target. This tendency substantially shifted toward the salient shape during saliency manipulation. Finally, by fitting choice data with multiple reinforcement learning models, we found that participants' choice behavior was best captured by a model in which attention biased both decision-making and learning processes. Overall, our results demonstrate that exogenous attention can significantly influence the trajectory of reward learning by altering how different pieces of information compete for credit assignment and for the control of choice behavior.

Disclosures: **A. Shahamati:** None. **J. Lim:** None. **S. Park:** None. **A. Soltani:** None.

Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

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Topic: H.10. Human Learning and Cognition

Support: NSF GRFP Fellow (ES)
NIH/NINDS R01 NS-021135 (RTK)
NIH/NINDS U19 NS-107609-01 (JL and RTK)

Title: Neural correlates of the Wisconsin Card Sorting Task at mesoscopic and microscopic scales

Authors: *E. SANDOVAL[1,2], I. SKELIN[6], B. RAM[7], P. ANSOMS[7], E. BARCLAY[3], J. ZHENG[8], M. R. DEWEESE[4,3], J. LIN[9], R. T. KNIGHT[5,3];
[1]Univ. Of California, Berkeley, Berkeley, CA; [2]Helen Wills Neurosci. Inst., [3]Neurosci., [4]Physics, [5]Psychology, UC Berkeley, Berkeley, CA; [6]Univ. Hlth. Network, Toronto, ON, Canada; [7]Neurol., [8]Dept. of Neurolog. Surgery and Biomed. Engin., [9]Dept. of Neurol., UC Davis, Davis, CA

Abstract: The Wisconsin Card Sorting Task (WCST) is commonly used to index executive function, decision-making and working memory. In WCST, participants are shown 4 cards that each have 3 unique features on them. One feature is correct, and participants are instructed to select the correct card. Participants receive feedback on whether the choice was correct or incorrect, implicitly providing information about the rule. After five correct trials in a row or eight out of the past ten correct trials, the rule will change without notifying the participant. It's well known that damage to the prefrontal cortex impairs performance on this task, but it is unclear how the dynamics between prefrontal cortex and hippocampus mediate task performance. To answer these questions and probe the neural correlates of learning a schema and feedback responses to correct vs incorrect trials, we collected intracranial sEEG recordings from microwires in 12 patients during epilepsy monitoring while patients completed a modified version of the task that was previously validated with undergraduates, and non-human primates. We used a demixed principal component analysis (dPCA) to characterize the population level information decodable in the broadband local field potentials (LFP) and found that feedback alone accounted for 12% of the variance. On a single neuron level, we found significant responses to feedback manifested as an increase in firing rate at around 700 ms following feedback. To further investigate feedback signals, we used a previously developed hidden Markov Model to model human behavior and obtain estimates of value for each feature on a trial-by-trial basis. From this, we obtain estimates of reward prediction error (RPE) and Bayesian surprise and use these as regressors to investigate differences between salience prediction errors, and inference signals. These results provide preliminary evidence of feedback encoding for learning rule schemas in human single neurons across orbitofrontal cortex, anterior cingulate cortex, and hippocampus.

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Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

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Title: Dopamine blockade blunts an impact of positive mood on reward sensitivity

Authors: *J. MICHELY[1], E. ELDAR[2], M. DUBOIS[3], J. HABICHT[4], T. U. HAUSER[5], R. J. DOLAN[6];
[1]Dept. of Psychiatry & Neurosciences, Charité - Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany; [2]Hebrew Univ. of Jerusalem, Tel Aviv, Israel; [3]Max Planck UCL Ctr. for Computat. Psychiatry and Ageing Res., London, United Kingdom; [4]Max Planck UCL Ctr. for Computat. Psychiatry and Ageing Research, Univ. Col. London, London, United Kingdom, London, United Kingdom; [5]Wellcome Trust Ctr. for Neuroimaging, London, United Kingdom; [6]Max Planck UCL Ctr., London, United Kingdom

Abstract: Rewards impact on how we feel, which can, in turn, shape our perception of subsequent outcomes. It is believed that catecholamines play a critical role in the interaction between mood and reward sensitivity, but the neuromodulatory mechanisms remain unclear. Here, in a double-blind, placebo-controlled, pharmacological study involving 60 healthy human volunteers, we examined the contribution of dopamine and noradrenaline to the dynamics of mood and reward sensitivity during learning. Specifically, we used antagonists of dopamine (400mg of amisulpride) and noradrenaline (40mg of propranolol) function, while tasking subjects on a probabilistic reward learning paradigm including a mood induction procedure and momentary mood assessments. Overall, we show that a large, unexpected reward elevates subjects' mood, where the magnitude of this mood response predicts a consequential boost in reward sensitivity during learning. Critically, a dopamine antagonist abolished this impact of positive mood on reward perception. By contrast, an antagonist of noradrenaline had no effect, suggesting the effect of dopamine blockade arises from a blunted impact of mood on reward sensitivity, and not from reduced arousal. Overall, our results shed light on the role of dopamine in mood dynamics and bring us closer to a mechanistic understanding of how dopamine antagonism leads to the clinical phenomenon of affective blunting over time.

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Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.11/T2

Topic: H.10. Human Learning and Cognition

Support: University of Melbourne Graduate Research Scholarships

Title: Who to learn from? The choice of information in observational reinforcement learning

Authors: *G. MORISHITA[1,2], S. SUZUKI[2,3], C. MURAWSKI[2], N. YADAV[4];
[1]Univ. of Melbourne, Carlton, Australia; [2]The Univ. of Melbourne, Parkville, Australia; [3]Fac. of

Social Data Sci., Hitotsubashi Univ., Tokyo, Japan; [4]The Univ. of Melborune, Parkville, Australia

Abstract: Reinforcement learning (RL) enables agents to predict the values of available options through trial and error. It involves updating the expected value of a chosen option based on their own reward experiences. To maximize rewards via RL, agents must balance the exploration of unfamiliar options for new information and the exploitation of the currently best option.People learn not only from their own experiences but also from others, referred to as observational learning. Recent studies in neuroscience have elucidated the computational and neural mechanisms underlying observational learning. People can learn the value of options by observing others' reward experiences, employing neurocomputational processes similar to those used in their own RL. However, much less is known about how individuals decide from whom to learn.Here, in this study, we hypothesized that people prefer to learn from other individuals who exhibit a higher degree of random exploration. This hypothesis stands on the reasoning that learning from high-explorative others allows for the exploration of unfamiliar options without missing their own opportunity to exploit the currently best option. An alternative hypothesis is that people prefer to learn from others with a lower degree of random exploration (i.e., a lower level of noise in decision-making). Learning from others with a lower noise-level could be beneficial if they aim to imitate the other individuals' choices.To test the hypotheses, we conducted a preregistered experiment using a novel behavioral task. In this experiment, participants (N = 55) first observed two potential partners performing a three-armed bandit task: one exhibited a higher level of random exploration, and the other exhibited a lower level. Participants then selected one of them as their partner for the subsequent observational learning task. Results of mixed-effect logistic regression analysis indicated that participants were more likely to prefer learning from individuals with a lower degree of random exploration (t(55) = -2.151, p = 0.036 two-tailed). In the presentation, we will further demonstrate the results of computational modeling. We believe our study provides significant insights into how humans accomplish social learning.

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Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.12/T3

Topic: H.10. Human Learning and Cognition

Support: BBRF Young Investigator Award
National Center for PTSD

Title: Biases in probabilistic learning strategy in trauma and posttraumatic stress disorder

Authors: *K. B. LOETSCHER[1], D. T. NGUYEN[1], J. H. KRYSTAL[2], E. V. GOLDFARB[1]; [1]Yale Univ., New Haven, CT; [2]Psychiatry, Yale Univ. Sch. of Med., New Haven, CT

Abstract: Posttraumatic stress disorder (PTSD) is a debilitating psychiatric illness, involving maladaptive cue avoidance and co-occurring alcohol use that may be driven by the formation of atypical, inflexible stimulus-response (SR) associations. Although such processes are associated with striatal function, this system is absent in prevailing memory models of PTSD. Evidence across species further suggests that striatal dependent SR learning is enhanced by stress. It remains unknown if such learning may similarly be enhanced in PTSD, and if these effects are linked to the pathology, or trauma exposure. We hypothesize that PTSD, not simply trauma exposure, will be associated with enhanced and more rigid SR learning, particularly for associations involving alcohol.

In an ongoing study, patients with PTSD (N = 25/35) and individuals who have experienced trauma but did not develop PTSD (trauma control [TC], N = 25/35), complete a multi-phase probabilistic learning task during an fMRI scan. In this task, participants learn to place each of 6 object stimuli (3 alcohol, 3 neutral) in the correct room, with optimal responses yielding a stimulus-unique positive outcome. After learning, there is an unsignaled reversal for 2/6 objects, in which the correct room changes, requiring participants to update their responses. In the final phase, outcomes associated with 2/6 other stimuli are "devalued" (attributed negative value), requiring participants to avoid associated stimuli.

A majority of participants (80%/group) successfully learned SR associations, performing significantly above chance. They also demonstrated successful reversal and sensitivity to outcome devaluation (choosing fewer devalued outcomes in a homologue of a consumption task, and changing response strategies to stimuli associated with devalued outcomes). Modeling optimal responses with a general linear model in learning reveals a main effect of group with post hoc tests revealing higher performance in the TC group, suggesting slower initial formation of SR associations in PTSD. These group differences are particularly pronounced when learning SR associations with alcohol cues. Despite slower learning, we find that SR associations are particularly rigid in PTSD, with more perseverative errors after reversal.

Ongoing analyses include leveraging computational learning models to quantify how learning and forgetting rates differ between groups. Neural analyses seek to investigate group differences in corticostriatal functional connectivity. Taken together, results suggest that PTSD may be associated with rigid SR associations over more flexible strategies.

Disclosures: K.B. Loetscher: None. **D.T. Nguyen:** None. **J.H. Krystal:** None. **E.V. Goldfarb:** None.

Poster

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Program #/Poster #: PSTR047.13/T4

Topic: H.10. Human Learning and Cognition

Support: NIH Grant R01 AG067011

Title: Age-related differences in neural responses to trust are associated with risk for financial exploitation

Authors: *C. J. SHARP[1], A. DACHS[1], J. B. WYNGAARDEN III[1], D. SAZHIN[1], I. KOHLI[1], A. HAWK[1], T. TROPEA[1], E. YANILMAZ[1], J. JARCHO[1], T. GIOVANNETTI[1], D. S. FARERI[2], D. V. SMITH[1];
[1]Psychology and Neurosci., Temple Univ., Philadelphia, PA; [2]Psychology, Adelphi Univ., Garden City, NY

Abstract: Social relationships influence our behaviors and may modulate our neural responses to reward. However, the effect of relationships on behavior and reward may change as we age. For example, reciprocated trust from a friend compared to a stranger is associated with enhanced ventral striatal (VS) activation (Fareri et al., 2015), though our recent work has suggested that this striatal response is blunted in older adults (Fareri et al., 2022). It remains unclear whether age-related differences in responses to trust are associated with maladaptive outcomes such as financial exploitation. To address this gap, we recruited participants (N = 101; ages 21-80 years; mean = 43.26 years) to play an economic trust game while undergoing fMRI. We also collected self-report questionnaires on risk for financial exploitation. In each round of the trust task, participants were allotted a sum of money ($8) and were presented with choices to invest a predetermined amount in one of three possible partners (friend, stranger, and computer). The money that participants decided to invest into their partner was then tripled, and the participant was shown whether their partner had split the money evenly with them (i.e., reciprocate) or kept the money for themselves (i.e., defect). Consistent with prior work from our group (Fareri et al., 2015; Fareri et al., 2022), we found that participants invested more with friends relative to strangers and computers. Preliminary fMRI analyses also showed increased activation in the VS during reciprocate relative to defect outcomes. In addition, the medial prefrontal cortex (MPFC) response to reciprocate relative to defect was enhanced when playing with friends compared to strangers, indicating that social closeness modulates responses in the MPFC. Interestingly, posterior cingulate cortex (PCC) responses to social closeness are positively correlated with the Older Adult Financial Exploitation Measure (OAFEM; Conrad et al., 2010). Taken together, these preliminary findings replicate and extend our prior work, showing that social relationships not only modulate neural responses to trust, but may play a role in vulnerability to financial exploitation.

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Poster

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Title: Thalamic regulation of reinforcement strategy switching across prefrontal-striatal networks

Authors: *B. WANG[1,2], N. H. LAM[3], S. LI[5], R. WIMMER[3], L. MENGXING[3], P. M. PAZ-ALONSO[6,7], M. HALASSA[3,4], B. PLEGER[2];
[1]South China Normal University, Sch. of Psychology, Guangzhou, China; [2]Dept. of Neurol., BG Univ. Hosp. Bergmannsheil, Ruhr-University Bochum, Bochum, Germany; [3]Dept. of Neurosci., [4]Dept. of Psychiatry, Tufts Univ. Sch. of Med., Boston, MA; [5]Dept. of Med. Imaging, Guangdong Second Provincial Gen. Hosp., GuangZhou, China; [6]Basque Ctr. On Cognition, Brain and Language, Donostia-San Sebastian, Spain; [7]Ikerbasque, Basque Fndn. for Sci., Bilbao, Spain

Abstract: In uncertain environments, agents can employ a mixture of two distinct reinforcement learning (RL) strategies: a flexible, forward-looking strategy referred to as model-based RL, and a computationally-efficient, stimulus-response strategy known as model-free RL. Despite their significance in adaptive behavior, the neural mechanisms governing the arbitration between these strategies remain elusive. Here, combining multimodal imaging data from humans with a probabilistic reversal task, we find a unique role for the mediodorsal thalamus (MD) in arbitrating between prefrontal (PFC) and striatal RL processes. While both dorsal PFC and striatum engage in strategy switching, the former does so when subjects adopt a predominant model-based strategy, while the latter model-free. MD, on the other hand, engages in both RL processes while exhibiting distinct functional connectivity profiles with PFC and striatum, contingent upon the adopted strategy. This thalamic involvement facilitates behavioral switching, with causal requirement and evolutionary homology suggested by optogenetic MD silencing in mice. Remarkably, regression analysis shows that model-based processing engages the lateral MD (MDl), which interacts with dorsal PFC structures shown by tractography and task-based functional analysis. Model free MD processing on the other hand appears to engage ventral PFC. Overall, our study unveils thalamocortical processes underlying the arbitration between large scale learning systems and perhaps a general role of the thalamus in regulating the interaction between evolutionary ancient and more recently evolved brain networks.

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Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

Location: MCP Hall A

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Program #/Poster #: PSTR047.15/T6

Topic: H.10. Human Learning and Cognition

Title: The impact of aging on the prioritization of information and reward during learning of a novel environment in a complex, sequential decision-making task

Authors: *A. HEDDEN[1], D. L. BARACK[4], A. BAKKOUR[1,2,3];
[1]Dept. of Psychology, [2]Inst. for Mind and Biol., [3]Neurosci. Inst., Univ. of Chicago, Chicago, IL;
[4]Dept of Neurosci. and Dept of Philosophy, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Healthy aging is long-associated with impairments in learning from environmental feedback. While computational reinforcement learning suggests environmental rewards drive this type of learning, typical paradigms do not adequately distinguish between information-related and reward-related motivations. The present study aimed to ascertain how these distinct motivations uniquely guide learning about one's environment in aging populations. Participants (N=169; ages 18-71 (*M*=39, *SD*=15.42)) completed a task based on the board game Battleship, making sequential choices about which tile to uncover on a grid with the goal of finding and learning hidden shapes. Analysis of participants' choices revealed that information was prioritized over rewards early in a trial, but this prioritization decreased as learning progressed. However, as age increased, selection of informative options persisted even after shapes were learned, revealing an age-dependent shift in motivations as learning progresses. Surprisingly, older participants learned the shapes faster, an unanticipated finding given the large literature linking age with decreased ability to learn from feedback. Finally, individuals adept at foraging for information learned more quickly than those who were worse, and increasing age was associated with better information foraging abilities. Our startling findings suggest aging may modulate the ways in which individuals search and learn from their environments when multiple motivations are available, helping aging adults to learn from the world around them. These findings challenge conventional assumptions about cognitive performance and aging, as older adults display an impressive aptitude to learn from feedback even in a complex environment so long as both information and reward are available as motivation. This insight not only deepens our understanding of feedback-based learning mechanisms but also sheds light on the nuanced interplay between aging and decision-making.

Disclosures: **A. Hedden:** None. **D.L. Barack:** None. **A. Bakkour:** None.

Poster

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Topic: H.10. Human Learning and Cognition

Support: R21AG072673
R01NS119468 (PI: ER Chrastil)

Title: Goal-directed control evolves in tandem with multiple task representations

Authors: *J. YOO[1,2], A. BORNSTEIN[3,4];
[1]UC Irvine: Univ. of California Irvine, Tustin, CA; [2]Department of Cognitive Sciences, University of California, Irvine, Irvine, CA; [3]Dept. of Cognitive Sci., Univ. of California, Irvine, Irvine, CA; [4]Center for the Neurobiology of Learning and Memory, University of California, Irvine, Irvine, CA

Abstract: When navigating complex tasks, it can be helpful to have multiple ways of looking at the problem. Emerging evidence suggests that humans and animals construct multiple distinct representations of their environments. How do these evolve as a result of our interactions with the environment, and how are they combined to support choices? Here, we examined how different kinds of memories for task structure were created and used as a function of experience, within-subject, and task complexity, across-subjects (total n=426). Participants performed a variant of the two-stage model-based planning task, in which first-stage choices could be selected from a variably-sized set of possibilities. Complexity favored representing the environment either as individual first-stage options or as combinations of them. Fitting choices and reaction times jointly with a new two-stage Reinforcement Learning-Drift Diffusion Model (RL-DDM), we examined how the components of planning time changed as individuals learned the space of possible options. We found, across four experiments, that planning time was best explained by a mixture of elemental and configural representations that evolved with experience in the task. This mixture favored the least complex representation at first, with a balance that shifted to more complex as uncertainty decreased. We also observed substantial individual variability in the transition from simple to complex, which we hypothesized may be due to differences in the ability to represent complex task structure. In a separate experiment (n=14), we examined how structural fidelity of key neural regions - hippocampus, associated with processing elemental and configural representations, and the caudate, which supports goal-directed behavior - are related to model-derived estimates of the difficulty of selecting among task representations. We observed that degraded structural integrity of hippocampus and caudate lowers sensitivity to task structure. This relationship could not be explained by other age-related factors. Taken together, our results suggest that the interactive updating and retrieval of representations for planning could vary according to different contingencies, and the potential role of hippocampus and the caudate involved in this process.

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Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

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Program #/Poster #: PSTR047.17/T8

Topic: H.10. Human Learning and Cognition

Support: NIDA K01DA053438

Title: Influences of reward on neural memory representations across development

Authors: *A. O. COHEN[1], C. PHANEUF[2], X. SHEN[3], L. DAVACHI[4], C. A. HARTLEY[5];
[1]Emory Univ., Atlanta, GA; [2]Harvard Univ., Cambridge, MA; [3]Temple Univ., Philadelphia, PA; [4]Psychology, Columbia Univ., New York, NY; [5]Psychology, New York Univ., Brooklyn, NY

Abstract: Rewards influence behavioral and neural memory processes. Recent research suggests that reward enhances memory through differential engagement of mesocorticolimbic systems across development. However, few studies have examined multivariate representations of reward memories, or whether these representations exhibit systematic changes across development. Prior work conducted in adults has shown that rewards alter hippocampal activation patterns during encoding and that cortical pattern similarity between encoding and retrieval is associated with better memory for both neutral and emotional stimuli. Still, how reward influences neural memory representations and whether there are developmental changes in reward-related memory representations remain unknown. To address these knowledge gaps, 89 participants ages 8 to 25 years-old completed a reward-motivated encoding and retrieval fMRI paradigm. We use representational similarity analysis to quantify and compare pattern similarity between individual high- and low-reward encoding and retrieval trials across age. Preliminary analyses suggest different age-related patterns of anterior hippocampal and visual cortical encoding-retrieval similarity (ERS) for high- relative to low- reward trials. This work will provide insights into how reward influences memory representations across development.

Disclosures: A.O. Cohen: None. **C. Phaneuf:** None. **X. Shen:** None. **L. Davachi:** None. **C.A. Hartley:** None.

Poster

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Topic: H.10. Human Learning and Cognition

Support: NIH R01MH133732

Title: Agency personalizes naturalistic event memories

Authors: *X. LI[1], N. K. NI[1], S. J. BORN[2], R. J. GUALANO[3], I. LEE[1], B. BELLANA[4], J. CHEN[1];
[1]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD; [2]Psychological and Brain Sci., Washington Univ. in St. Louis, St. Louis, MO; [3]Dept. of Communication, Cornell Univ., Ithaca, NY; [4]York Univ., Glendon Col., Toronto, ON, Canada

Abstract: In daily life, we continually make choices that create a chain of events, shaping the narrative of our personal history and guiding our memory. However, laboratory experiments on memory using narratives typically do not allow participants to direct the story. We investigated how agency affected memory for narratives using two interactive stories, *Adventure* (N=116) and *Romance* (N=208). Participants were divided into three conditions: ‘Free’ (made influential

choices), 'Yoked' (made choices but some were denied), or 'Passive' (made no choices), as they read the same stories. We found that event recall was predicted by semantic and causal connectedness to other events ("centrality") across all conditions in both stories (all *p*s < .001). Agency selectively reduced the effect of semantic centrality on memory (*Adventur*e: $F(2,113) = 3.04$, $p = 0.052$; *Romance*: $F(2,123) = 11.46$, $p < 0.001$), while the effect of causal centrality on memory was not different across conditions. Further analysis revealed that agency altered subjects' event-by-event memory in both systematic and idiosyncratic ways. Specifically, agency systematically enhanced the tendency for participants to recall neighboring events (*p*s < 0.001). Meanwhile, agency also increased individual variability in event-by-event memory: Free subjects were significantly less similar to one another in terms of which events they remembered, compared to Yoked and Passive (*p*s < 0.001). Furthermore, the three effects in Free subjects were related to each other: the magnitude of 1) reduction in the impact of semantic centrality on memory, 2) the increased tendency to recall neighboring events, and 3) the increased idiosyncrasy of memory, were positively correlated. In a regression model, the latter two each explained unique variance when predicting the reduced impact of semantic centrality on memory (neighbor effect: $b = -.12$, $p = .014$; idiosyncratic effect: $b = -.38$, $p < .001$). Overall, this study demonstrated that having agentive control over narratives impacted the way that semantic structure guided memory, caused events to be recalled more idiosyncratically, and strengthened relations between adjacent events, offering new insights into the organization of human memory in real-life scenarios.

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Poster

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Program #/Poster #: PSTR047.19/T10

Topic: H.10. Human Learning and Cognition

Support: R01 29365

Title: Neural correlates of decision uncertainty and memory enhancement during hypothesis testing

Authors: *X. SHEN[1], D. V. SMITH[2], V. P. MURTY[3];
[1]Temple Univ., Philadelphia, PA; [2]Dept. of Psychology & Neurosci., Temple Univ., Philadelphia, PA; [3]Psychology, Temple Univ., Philadelphia, PA

Abstract: Humans are motivated to actively seek information to reduce uncertainty, which we have previously shown to alter episodic memory. Specifically, we found that uncertainty during hypothesis testing was both linearly and quadratically related to episodic memory. Yet, little is known about the neural mechanisms underlying how hypothesis testing relates to subsequent

memory. During the collection of fMRI data, 40 participants were presented with three multi-dimension keys, and participants were instructed to figure out the target feature of a key to open a treasure chest. The target feature changed after four consecutive choices of the stimulus with the target feature. RL modeling was used to capture an individual's decision uncertainty around different features of the keys. We found that decreasing decision uncertainty was related to greater activation in the ventral striatum, anterior hippocampus, and ventromedial prefrontal cortex (VMPFC) (ROI analysis, *p*s < 0.01). Further, the activity in the anterior hippocampus (ROI analysis, $p = 0.03$) and the posterior hippocampus (ROI analysis, $p = 0.02$) was greater for subsequently remembered versus forgotten items. In summary, our findings highlighted the significance of the ventral striatum, hippocampus, and VMPFC in representing decision uncertainty during hypothesis testing. Notably, activations in the anterior and posterior hippocampus were crucial for enhanced memory associated with decision uncertainty. Future work will investigate which regions track the subsequent memory and non-linear changes in decision uncertainty.

Disclosures: X. Shen: None. **D.V. Smith:** None. **V.P. Murty:** None.

Poster

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Topic: H.10. Human Learning and Cognition

Support: Duke Germinator Award to AHS
Duke Health Scholars Award to RAA

Title: Motivational states shape neural representations during reinforcement learning and memory formation

Authors: *A. H. SINCLAIR[1], Y. WANG[2], R. ADCOCK[3];
[1]Ctr. for Science, Sustainability, and the Media, Univ. of Pennsylvania, Philadelphia, PA;
[2]Psychology & Neurosci., [3]Psychiatry and Behavioral Sci., Duke Univ., Durham, NC

Abstract: Motivation influences goals, decisions, and memory formation. Imperative motivation links urgent goals to actions, narrowing the focus of attention and memory. Conversely, interrogative motivation integrates goals over time and space, supporting rich memory encoding for flexible future use. In an fMRI study with human participants (N=56, ages 18-35, 31 women), we modulated motivational states via cover stories: The imperative group imagined executing a museum heist, whereas the interrogative group imagined planning a future heist. During a subsequent reinforcement learning task, participants repeatedly chose among four doors (choice phase), representing different museum rooms, to sample trial-unique paintings with variable rewards (feedback phase). Rewards earned during reinforcement learning were converted to a bonus payment; participants in both groups had the same expectations about how

and when they would earn bonus payments. The next day, participants performed a surprise memory test on the paintings. Replicating our prior behavioral findings, we showed that motivational states shift the balance between short-term reward learning and long-term memory formation. Imperative motivation increased exploitative choices, learning rate, points earned, and optimal choices. Conversely, Interrogative motivation enhanced directed exploration (i.e., choosing to resolve uncertainty) and next-day recognition memory. fMRI results indicated differences in neural activation across groups. vmPFC activation during the choice phase paralleled the explore-exploit tradeoff observed in choice behavior: in the Imperative group, vmPFC activation predicted exploitation; in the Interrogative group, there were stronger representations of uncertainty in the vmPFC. Results from the feedback phase demonstrated that these motivational states are associated with distinct routes to memory formation. In the Interrogative group, VTA activity was modulated by reward and predicted subsequent recognition memory. In the Imperative group, greater right amygdala activation predicted subsequent recognition memory. Overall, we demonstrate that motivational states impact reinforcement learning and subsequent memory, shape neural representations of uncertainty and reward, and pave different routes to long-term memory formation. Our findings offer broader implications for enhancing education, behavior change, clinical interventions, and communication.

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Poster

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Topic: H.10. Human Learning and Cognition

Support: NIH R01 DA055259

Title: Characterizing the granularity of neural representations of reward-motivated memories.

Authors: *V. P. MURTY;
Univ. of Oregon, Eugene, OR

Abstract: Using behavioral modeling, we recently showed that reward-motivated memories are hierarchically organized around value categories (Horwath et al., 2023), such that individuals cluster high- versus low-value items together during free recall. Given these findings, we hypothesized that subsequently remembered high-value items should be represented more similarly than high-value forgotten items and all low-value items. However, extant research has yet to characterize if and where this type of neural organization exists. In this study, we scanned 29 individuals during a reward-motivated memory encoding paradigm, in which object images were either paired with high value (8-10 points) or low value (1-3 points). Representational similarity analysis was used to assess whether items sharing the same value were represented

more similarly, and whether this differed across high and low value categories. In the anterior hippocampus we found greater similarity amongst remembered versus forgotten items ($p<0.001$), however, this relationship did not vary by reward category. We found a double dissociation across large-scale memory networks outside of the hippocampus. In Anterior-Temporal networks there was greater similarity for high-value remembered items versus high-value forgotten and all low-value items ($p<0.001$), while in Posterior-Medial networks there was the greatest similarity for the lowest-value remembered items compared to higher-value items regardless of memory success ($p<0.05$). Together, these findings suggest that behavioral clustering of high-value items could be driven by shared representations in anterior temporal networks.

Disclosures: V.P. Murty: None.

Poster

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Topic: H.10. Human Learning and Cognition

Support: National Institute on Deafness and Other Communication Disorders (R01DC015426)
Intramural Research Program at the National Institute on Drug Abuse (ZIA DA000642)

Title: Anterior and posterior lateral OFC networks make dissociable contributions to stimulus-outcome learning and goal-directed choice

Authors: *Q. LIU[1], D. PORTER[2], H. DAMRA[2], Y. ZHAO[1], T. KAHNT[1];
[1]Natl. Inst. on Drug Abuse, Baltimore, MD; [2]Northwestern Univ., Chicago, IL

Abstract: Previous work across species has implicated the lateral orbitofrontal cortex (OFC) in guiding reward learning and goal-directed behaviors. However, the lateral OFC is a large and anatomically heterogeneous area, and the precise roles of its subregions remain largely unexplored. Here, we investigated the contributions of the anterior (aOFC) and posterior (pOFC) portions of the lateral OFC in reward learning and goal-directed behaviors. 48 fasted human subjects (15 males) completed a 3-session x 2-day outcome devaluation experiment with transcranial magnetic stimulation (TMS). On day 1 of each session, subjects learned associations between visual stimuli and food odor rewards. For a given pair of stimuli, one stimulus predicted a sweet or savory food odor, whereas the other stimulus predicted no reward. On day 2, subjects first consumed a meal that was matched to either the sweet or savory food odor (counter-balanced), decreasing the pleasantness of the food-matched (i.e., sated) odor. Then subjects made choices among visual stimuli predicting non-sated or sated odors. A preference for choosing stimuli predicting non-sated over sated odors indicates goal-directed choice. To probe the differential roles of lateral OFC subregions, we targeted aOFC and pOFC either before learning

the stimulus-outcome associations on Day 1 or before the meal and choice test on Day 2. To selectively target the aOFC and pOFC (in different groups of subjects), we used resting-state fMRI connectivity analyses to individually select stimulation sites in right lateral prefrontal cortex (LPFC) that were maximally connected to seed regions in the aOFC and pOFC, respectively. We applied continuous theta burst stimulation (cTBS) to temporarily disrupt brain network function over these stimulation sites. Targeting the aOFC network disrupted learning of stimulus-outcome associations on Day 1, whereas targeting the pOFC network had no effect compared to sham TMS. Conversely, targeting the pOFC network disrupted goal-directed choices on Day 2, whereas targeting the aOFC network had no effect relative to sham TMS. These results reveal distinct contributions of anterior and posterior portions of the lateral OFC to reward learning and goal-directed choice.

Disclosures: Q. Liu: None. **D. Porter:** None. **H. Damra:** None. **Y. Zhao:** None. **T. Kahnt:** None.

Poster

PSTR047: Human Feedback, Reinforcement, and Reward Learning

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.23/Web Only

Topic: H.10. Human Learning and Cognition

Support: Harvard University
National Defense Science and Engineering Graduate Fellowship

Title: Characterizing how emotion and reward information influence learning through adolescence

Authors: *C. V. PHANEUF[1], E. A. PHELPS[2], L. H. SOMERVILLE[3];
[1]Dept. of Psychology, Harvard Univ., Cambridge, MA; [2]Harvard Univ., Cambridge, MA, ;
[3]Dept. of Psychology & Ctr. for Brain Sci., Harvard Univ., Cambridge, MA

Abstract: To behave adaptively, individuals of all ages must heed value information in their environments. This study examines how incidental and integral value cues shape learning from childhood to adulthood (N = 114, 8-22 years). Within a probabilistic reinforcement learning task, emotional expressions conveyed incidental information while monetary rewards conveyed integral information. In some conditions, emotion and reward contributed to value in a congruent manner: following either cue promoted learning. In other conditions, emotion and reward contributed to value in an incongruent manner: following the emotion cue impeded reward learning. Based on previous research, we predicted that emotion information would modulate reward learning most in either adults or adolescents: while adults rely on supplemental information sources to infer reward value more than their child and adolescent counterparts, adolescents experience heightened emotional processing relative to children and adults. To adjudicate between these two hypotheses and characterize age-related changes in the influence of

emotion and reward information on choice, we fit logistic mixed-effects models and temporal difference reinforcement learning models to participants' decisions in the task. These analyses revealed that although participants of all ages adopted condition-wise learning strategies, younger participants' learning was most disrupted by emotion-reward incongruency. Meanwhile, older participants leveraged emotion-reward congruency to guide their choices to the greatest degree. Together, this work suggests that the flexible use of incidental and integral information to engage in context-appropriate learning increases with age.

Disclosures: C.V. Phaneuf: None. **E.A. Phelps:** None. **L.H. Somerville:** None.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.01/U2

Topic: I.03. Anatomical Methods

Title: Combining Electrophysiology, Tissue Clearing, and Light Sheet Microscopy for an integrated approach towards brain circuit understanding

Authors: *S. BÖHM[1], H.-U. DODT[2];
[1]Section for Bioelectronics, Med. Univ. of Vienna: Ctr. for Brain Res., Vienna, Austria; [2]Tech. Univ. Vienna, Wien, Austria

Abstract: Traditional histological techniques, which require imaging of individual tissue sections, are widely used but tend to be error-prone, time-consuming, and can lead to section loss or non-uniform deformation. Optical sectioning provides a faster and simpler alternative. For instance, light sheet fluorescence microscopy enables the production of high-resolution images of entire brains. This project aimed to use light sheet fluorescence microscopy as a complementary technique to visualize juxtacellular recorded and labeled neurons in anesthetized rats. Our novel approach involved labeling a single neuron in a rat brain with neurobiotin using the juxtacellular recording and labeling technique. Afterwards, we cleared the brain using an innovative 3DISCO protocol and subsequently imaged using light sheet microscopy. Following imaging, the neuron was three-dimensionally reconstructed with Amira software for comprehensive analysis, measurement, and 3D visualization. Our preliminary results introduce a novel clearing protocol designed specifically for rat brains, representing the fusion of single cell labeling with behavioural assays and tissue clearing. To conclude, this study represents a novel technical approach. It uniquely integrates electrophysiology with a well-known optical sectioning imaging method, the so-called light sheet fluorescence microscopy. This methodology not only improves the efficiency and precision of whole-brain imaging but also allows for detailed neuronal analysis and visualization, contributing to our comprehension of brain function and structure.

Disclosures: S. Böhm: None. **H. Dodt:** None.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.02/U3

Topic: I.03. Anatomical Methods

Support: NIH R01 AG079193

Title: Label-free Two Photon Autofluorescence Imaging of Amyloid-Beta plaques

Authors: *S. A. SUAREZ[1], J. VILLANUEVA[2], A. GENTILE POLESE[5], A. VILLEGAS-LANAU[6], F. LOPERA[6], E. GIBSON[3], D. RESTREPO[4];
[1]Univ. of Colorado Anschutz Med. Campus Grad. Sch., Aurora, CO; [2]Cell and Developmental Biology, Neurol., [3]Bioengineering, [4]Cell and Developmental Biol., Univ. of Colorado Denver Anschutz Med. Campus, Aurora, CO; [5]Cell and Developmental Biol., Univ. of Colorado Anschutz Med. Campus, Aurora, CO; [6]Neurosci. Res. Group, Univ. of Antioquia, Medellin, Colombia

Abstract: A hallmark of Alzheimer's disease (AD) is the aggregation of Amyloid-β (Aβ) proteins into insoluble plaques. They deposit themselves into neural tissue and interfere with normal neuronal function and are thought to lead to neurodegeneration over time. Current Aβ imaging methods rely on fluorescent markers and immunohistochemical stains. Our research explores the range and quality of intrinsic autofluorescence signals from plaques using two photon microscopy (2PM). Compared to conventional fluorescence microscopy techniques, 2PM offers good resolution without external stains, deep tissue penetration, low photodamage, and three-dimensional imaging of plaques. We report on progress toward imaging Aβ plaques in 5xFAD mice and human familial AD brain tissue samples.

Disclosures: S.A. Suarez: None. **J. Villanueva:** None. **A. Gentile Polese:** None. **A. Villegas-Lanau:** None. **F. Lopera:** None. **E. Gibson:** None. **D. Restrepo:** None.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.03/U4

Topic: I.03. Anatomical Methods

Support: JSPS KAKENHI JP21H02592
AMED JP21dm0207112

JST JPMJMS2024
JST JPMJFR204D
JSPS KAKENHI JP23K20044
JSPS KAKENHI JP23K06310
JSPS KAKENHI JP23K21711
JSPS KAKENHI JP22K19403

Title: Multi-scale brain-to-synapse imaging with a tissue clearing method, scalesf.

Authors: *H. HIOKI[1,2,3], K. YAMAUCHI[1,2], T. FURUTA[4];
[1]Dept. of Neuroanatomy, Grad. Sch. of Med., Juntendo Univ., Tokyo, Japan; [2]Department of Cell Biology and Neuroscience, Graduate School of Medicine, Juntendo University, Tokyo, Japan; [3]Department of Multi-Scale Brain Structure Imaging, Graduate School of Medicine, Juntendo University, Tokyo, Japan; [4]Dept. of Systematic Anat. and Neurobio., Grad. Sch. of Dent., Osaka Univ., Suita-Shi, Japan

Abstract: The mammalian brain contains a heterogeneous mixture of billions of neurons with trillions of synapses. Connectomics, a description of wiring diagram of the nervous system, is fundamental for understanding how a neural circuit processes information and generates behavior. While neurons elaborate highly specialized processes that can span over a meter in length, synapses that connect neurons are several hundred nanometers in size. Thus, the imaging scale required for deciphering brain-wide connectivity exceeds several orders of magnitude. Our study overcomes the technical requirements required for whole-brain and nanoscale imaging by coupling a tissue clearing method with successive light (LM) and electron microscopy (EM) imaging (multi-scale LM/EM neuronal imaging). We have established an imaging pipeline that enables correlative light and electron microscopy (CLEM) in optically cleared tissues in this study (Fig). Our multi-scale neuronal imaging makes it possible to describe synaptic connectivity of brain-wide circuits by simultaneous interrogation of the neural circuit structure mapped in optically cleared brain tissues, and synaptic connectivity imaged with EM in a reasonable amount of time, without the need for specialized equipment. Our study has expanded the applicability of tissue clearing techniques from LM to EM by developing an ultrastructurally-preserved tissue clearing method, Sca*l*eSF, and implementing LM/EM dual labeling that remained stable in the clearing protocol. We believe that our technique will contribute to our understanding of brain-wide connectivity beyond the reach of current connectomic analyses with a single imaging modality.

Disclosures: **H. Hioki:** None. **K. Yamauchi:** None. **T. Furuta:** None.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.04/U5

Topic: I.03. Anatomical Methods

Support: National Research Foundation of Korea (NRF-2021R1I1A1A01046548)
National Research Foundation of Korea (NRF- RS-2023-00278593)
the Ministry ofHealth & Welfare, Republic of Korea (HI23C1469)
the Catholic Medical Center Research Foundation program year of 2022

Title: Optimized Fixation and Autofluorescence Reduction Methods for Correlative Light and Electron Microscopy in Postmortem Human Brain Tissue

Authors: *A. CHO[1], D.-G. KIM[1,2], H.-L. KIM[3], J.-W. HWANG[1,2], R. T. HAN[4,5], M.-Y. LEE[1,2], T.-R. T. RIEW[1,2];
[1]Dept. Of Anat., Catholic Neurosci. Inst., Col. Of Med., The Catholic Univ. Of Korea, Seoul, Korea, Republic of; [2]Department of Biomedicine and Health Science, College of Medicine, The Catholic University of Korea, Seoul, Korea, Republic of; [3]Integrative Res. Support Ctr., Lab. of Electron Microscope, Col. of Med., Seoul, Korea, Republic of; [4]Biomed. Res. Div., Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [5]KIST Department of Converging Science and Technology, Kyunghee University, Seoul, Korea, Republic of

Abstract: Correlative light and electron microscopy (CLEM) is a powerful tool for investigating the relationship between molecular and ultrastructural features in biological samples. However, the application of CLEM to postmortem human brain tissue presents challenges in preserving ultrastructure, maintaining immunogenicity, and reducing autofluorescence. In this study, we compared three fixation methods for postmortem human hippocampus, medial prefrontal cortex, and dural meninges: 1) 4% paraformaldehyde (PFA), 2) 4% PFA with 0.2% glutaraldehyde, and 3) 2.5% glutaraldehyde. For the first two methods, we employed a modified Tokuyasu technique for cryopreservation and CLEM analysis. We also investigated the effectiveness of sodium borate and Sudan Black B in reducing autofluorescence for light microscopic imaging. Semi-thin sections were prepared using an ultramicrotome, and immunohistochemistry (IHC) was performed to compare immunolabeling specificity and sensitivity. Furthermore, we assessed the ultrastructural quality of the samples fixed with 4% PFA with 0.2% glutaraldehyde followed by transmission electron microscopy (TEM) preparation and compared it to the conventional 2.5% glutaraldehyde fixation and EM preparation. Our results demonstrated that 4% PFA with 0.2% glutaraldehyde fixation preserved immunogenicity of key marker proteins in semi-thin IHC settings. Although sodium borate and Sudan Black B reduced autofluorescent signals, they also diminished specific IHC signals in semi-thin sections. Importantly, 4% PFA with 0.2% glutaraldehyde fixation maintained ultrastructural quality comparable to 2.5% glutaraldehyde fixation immediately after tissue harvesting. These findings provide an optimized methodology for CLEM analysis of postmortem human brain tissue, balancing the preservation of ultrastructure, immunogenicity, and reduction of autofluorescence.

Disclosures: **A. Cho:** None. **D. Kim:** None. **H. Kim:** None. **J. Hwang:** None. **R.T. Han:** None. **M. Lee:** None. **T.T. Riew:** None.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.05/U6

Topic: I.03. Anatomical Methods

Support: Fondazione CR Firenze, Human BrainOptical Mapping
NIH grant U01 MH117023
EBRAINS
Italian Ministry for Education in the framework of Euro-Bioimaging Italian Node

Title: 3d reconstruction and cellular phenotyping on deparaffinized human brain tissues

Authors: *D. DI MEO[1], M. SORELLI[2], G. MAZZAMUTO[4], J. RAMAZZOTTI[5], F. CHELI[3], B. LORENZON[5], F. S. PAVONE[6], I. COSTANTINI[7];
[1]LENS- European Lab. for Non-Linear Spectroscopy, Sesto Fiorentino, Italy; [2]Dept. of Physics and Astronomy, Univ. of Florence, [3]LENS - European Lab. for Non-linear Spectroscopy, Univ. of Florence, Sesto Fiorentino, Italy; [4]CNR-INO and LENS, Sesto Fiorentino, Italy; [5]LENS - European Lab. for Non-linear Spectroscopy, Univ. of Florence, Sesto Fiorentino, Italy; [6]Univ. Florence, Sesto Fiorentino (FI), Italy; [7]Dept. of Biol., LENS - Univ. of Florence, Sesto Fiorentino, Italy

Abstract: Characterizing the three-dimensional (3D) cytoarchitecture of human brain areas remains a challenging task due to the complexity of the biological composition, the variability in fixation and storage conditions and the limited availability of human samples. Unlike traditional histopathological methods, which are limited to two-dimensional representations, 3D analysis offers a comprehensive understanding of the spatial organization of human brain areas, enabling researchers to capture the full complexity of biological structures and correlate to their function. Formalin-Fixed Paraffin-Embedded (FFPE) specimens, commonly used for standard histological analysis, represent a significant yet underutilized resource for advanced volumetric analysis. However, volumetric reconstruction of human brain areas with fluorescence techniques, such as light-sheet fluorescence microscopy (LSFM) or two-photon fluorescence microscopy (TPFM), requires tissue optical transparency. Here, we present a comprehensive pipeline to perform 3D imaging and automated analysis on FFPE human brain specimens. This workflow includes human brain tissue deparaffinization, optical clearing, multi-labeling, LSFM or TPFM imaging, and automated neuronal segmentation. To harness the full potential of clearing techniques on FFPE samples, an essential step in the workflow involves the full removal of the paraffin matrix that could interfere with subsequent clearing and labeling steps. Therefore, we optimized a mild deparaffinization method that preserves tissue integrity and protein structure and works on blocks of human brain tissue of different sizes. This method was applied on adult post-mortem human brain areas (Brainstem and Hippocampus) and surgically removed brain specimens from pediatric patients. Deparaffinized samples were processed with the SHORT clearing and labeling method, followed by 3D volumetric reconstruction obtained either with inverted LSFM (3.6 µm isotropic resolution) or TPFM custom-made setups (1.2 × 1.2 × 2 µm resolution). A machine-learning-based image segmentation tool was used to analyze the brain tissue reconstructions, obtaining quantitative information on the spatial distribution and morphology of different classes of neurons, thus highlighting the differences between various pathological samples. Overall, this approach grants access to a wide range of paraffin-embedded clinical specimens to perform 3D

volumetric analysis with cellular resolution, enabling unprecedented insights into human tissue cytoarchitecture for both physiological and pathological samples.

Disclosures: **D. Di Meo:** None. **M. Sorelli:** None. **G. Mazzamuto:** None. **J. Ramazzotti:** None. **F. Cheli:** None. **B. Lorenzon:** None. **F.S. Pavone:** None. **I. Costantini:** None.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.06/U7

Topic: I.03. Anatomical Methods

Support: Department of Psychology, Illinois State University

Title: Strategies to improve immunohistochemical staining for tryptophan hydroxylase in fixed rat brain medulla

Authors: *B. A. HEIDENREICH, A. MCLARTY;
Psychology, Illinois State Univ., Normal, IL

Abstract: Tryptophan hydroxylase (TpOH) is the first enzyme in the synthesis of serotonin and is often used as a marker for serotonergic activity. Immunohistochemistry for TpOH is widely done to identify serotonin neurons in brain. Upon starting research examining TpOH in rat brain medulla, we performed a series of variations in our immunostaining protocol to try to improve the quality of specific staining and reduce the amount of non-specific (background) staining. Forty micron thick sections of medulla were cut with a cryostat microtome from rats transcardially perfused with 0.9% saline and 4% p-formaldehyde in 0.1 M phosphate buffer (PB). Brains were post-fixed 24 h in p-formaldehyde and cryoprotected in 20% sucrose in 0.1 M PB. All reagents were obtained from Sigma-Aldrich unless noted. Sections were washed in phosphate-buffered saline (PBS) before and between all steps. Tissues were treated with 0.4% H_2O_2 in methanol for 20 min to quench endogenous peroxidase activity and with 1% sodium borohydride in 0.1 M PB for 30 min to enhance permeability of the tissue and improve staining. Sections were then treated with horse serum (Sigma-Aldrich or Vector Labs) in PBS with 0.2% Triton X-100 detergent for 1 h and either 0.8% bovine serum albumin (Fisher) in PBS or PBS alone for 40 min. Tissues were incubated in mouse monoclonal anti-TpOH antibody (1:1000) in PBS with 0.3% Triton X-100 and horse serum. Some sections were incubated without the primary antibody (omit negative controls). Forty-eight h later, tissues were treated with biotinylated horse anti-mouse antibody and then avidin-biotin-peroxidase complex (ABC; Vector Elite kit), both in PBS with 0.3% Triton X-100 and horse serum for either 30 or 60 min. All sections were reacted with 0.0005% diaminobenzidine with 0.0001% H_2O_2 for 60 - 90 sec, mounted on gelatin-coated slides, dehydrated and coverslipped with DPX. Stained and negative control sections were examined using standard light microscopy. Specific immunostaining for TpOH was notably greater than background staining. Treatment with albumin prior to primary

antibody incubation did not alter TpOH staining. In omit control sections, neither albumin or separate avidin and biotin pretreatments (Vector) reduced background staining. Increasing the duration of secondary antibody and ABC treatments from 30 to 60 min increased background staining. Finally, the use of horse serum from Vector produced lower non-specific staining than serum from Sigma. We continue to test methods to improve our protocol for TpOH immunohistochemistry.

Disclosures: B.A. Heidenreich: None. **A. McLarty:** None.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.07/U8

Topic: I.03. Anatomical Methods

Support: SBIR Grant R44MH119989
SBIR Grant R43MH122070

Title: Exploring Tissue Clearing: Advantages and Applications in Neuroscience

Authors: *N. GUANZON[1], C. REDD[1], E. BLAES[1], Y. GALLEGOS[1], E. CASTILLO[1], R. AZEVEDO[2,1], D. G. WHEELER[1];
[1]Translucence Biosystems, Irvine, CA; [2]UC Irvine, Irvine, CA

Abstract: Traditional histological methods have long been fundamental to neuroscience research. However, imaging deep into tissues has historically required slicing and mounting on slides, limiting observations to predefined regions of interest. Tissue clearing revolutionizes this approach, offering neuroscientists comprehensive views of tissue anatomy and function. While scientifically and statistically relevant, wide adoption of tissue clearing has been slow. In this poster, we demonstrate how tissue clearing enables unbiased quantification of intact 3D biological samples. We use our iDISCO-based tissue clearing reagent kits, a ZEISS Lightsheet Z.1 microscope equipped with our Mesoscale Imaging System, and our AI-powered quantification software, the Translucence Teravoxel Toolkit (3TK), to analyze terabyte-scale datasets across various tissue types and target epitopes. Our optimized imaging methods allow for micron-scale resolution imaging of entire intact mouse brains in under 20 minutes. Further, our AI-powered software, 3TK, identifies individual immunostained cells and objects throughout the sample. In the case of the brain, we can use our in-house alignment algorithms with the Allen Reference Atlas to produce unbiased, regionalized read-outs of object patterns across 100’s brain areas. These techniques are especially valuable in drug development, allowing for the examination of regional distribution, target engagement, and the efficacy of novel therapeutics, and are also advantageous in a wide variety of neuroscientific studies that would benefit from understanding systems-level biology and 3D structure visualization. Here, we will explore datasets that outline the power of tissue clearing in studying the nervous system, aiming to

discuss with neuroscientists how tissue clearing and its unbiased insights into systems-level biology might be applicable in their research.

Disclosures: N. Guanzon: A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **C. Redd:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **E. Blaes:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **Y. Gallegos:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **E. Castillo:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **R. Azevedo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **D.G. Wheeler:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.08/U9

Topic: I.03. Anatomical Methods

Support: This research was supported in part by the Illinois Computes project which is supported by the University of Illinois Urbana-Champaign and the University of Illinois System.
This work was supported by the Student Sustainability Committee of the University of Illinois Urbana-Champaign and the Illinois Green Fund.

Title: Anatolution: a community platform for consensus neuroanatomy

Authors: *D. J. MILLER;
Evolution, Ecology, and Behavior, Univ. of Illinois, Urbana, IL

Abstract: The advent of noninvasive neuroimaging has increased the need for ground-truth comparisons to histology to improve diagnostics and therapeutics of the brain for a range of conditions. Historically, quantitative histology using stereology had not been feasible at the level

of the whole brain for direct comparison to magnetic resonance imaging (MRI), but the advent of deep learning on supercomputers provides a novel opportunity to develop higher-throughput anatomical methods. To provide biologically meaningful information, these methods unfortunately require deep datasets of the highest quality, necessitating the development of tools where domain experts can generate and export custom machine-readable files. The backbone of the Anatolution platform is built in Python, the database hosted on Heroku, the images stored in Amazon Web Services S3, and we use Open Computer Vision along with Pandas for label creation and data management. We make our platform for custom for human in the loop consensus annotations available as a resource to the community by contacting registration@vivoture.com to join. Following account creation, scholars can link to files, create projects, design annotations, and then download their label data. The Anatolution platform for community neuroanatomy represents a novel framework to construct the next generation of quantitative morphometric methods by leveraging consensus among domain experts to train and calibrate deep learning models to scale histology. Ultimately, this project seeks to build a community and in doing so support the continued development of quantitative histological methods to address the burgeoning need for direct multiscale comparisons of brain structure and function with clinically relevant methods like neuroimaging.

Disclosures: D.J. Miller: None.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.09/U10

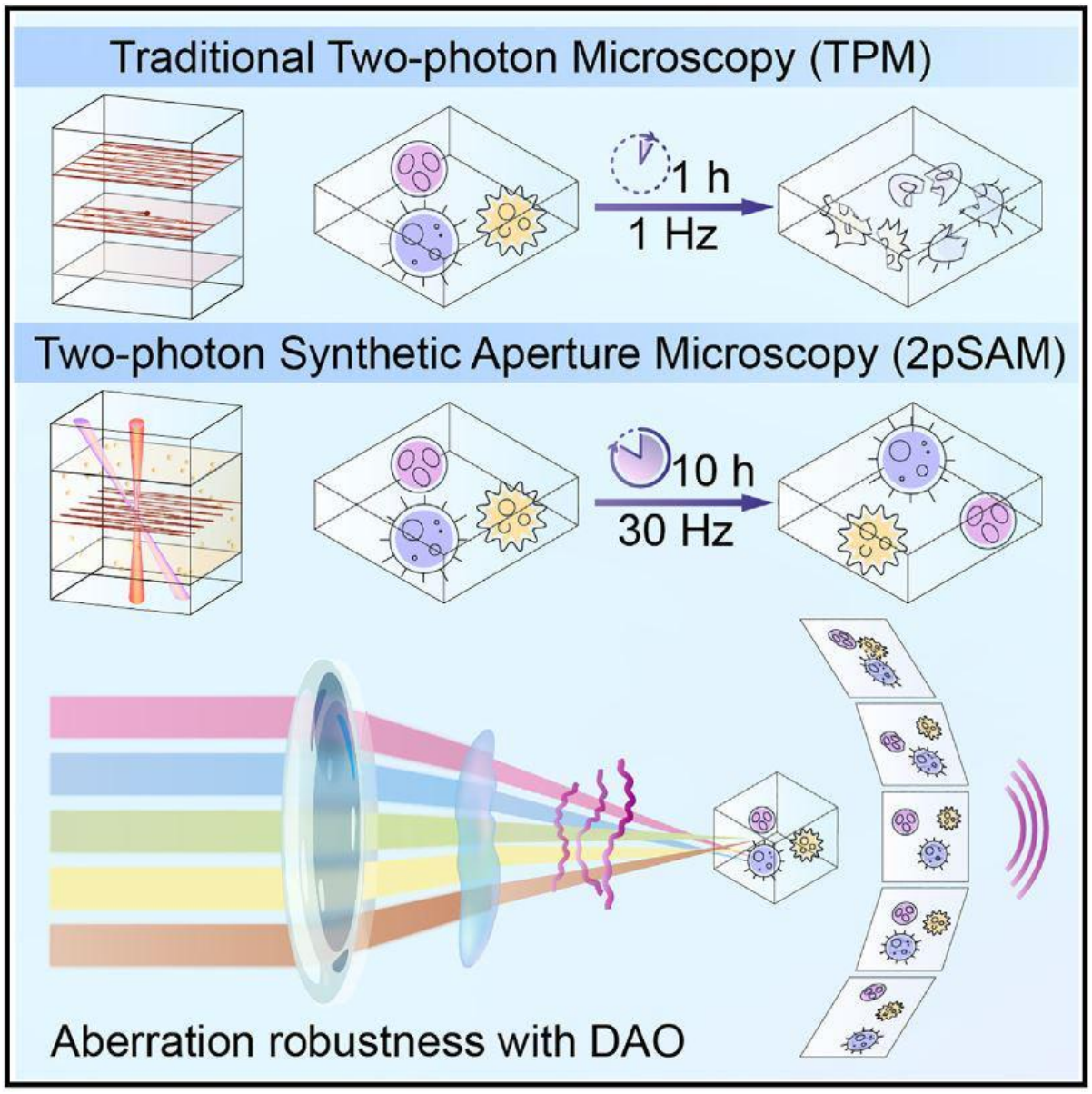
Topic: I.03. Anatomical Methods

Title: Two-photon synthetic aperture microscopy for minimally invasive fast 3D imaging of native subcellular behaviors in deep tissue

Authors: *Z. ZHAO, J. WU, Q. DAI;
Tsinghua Univ., Beijing, China

Abstract: Holistic understanding of physio-pathological processes requires noninvasive 3D imaging in deep tissue across multiple spatial and temporal scales to link diverse transient subcellular behaviors with long-term physiogenesis. Despite broad applications of two-photon microscopy (TPM), there remains an inevitable tradeoff among spatiotemporal resolution, imaging volumes, and durations due to the point-scanning scheme, accumulated phototoxicity, and optical aberrations. Here, we harnessed the concept of synthetic aperture radar in TPM to achieve aberration-corrected 3D imaging of subcellular dynamics at a millisecond scale for over 100,000 large volumes in deep tissue, with three orders of magnitude reduction in photobleaching. With its advantages, we identified direct intercellular communications through migrasome generation following traumatic brain injury, visualized the formation process of germinal center in the mouse lymph node, and characterized heterogeneous cellular states in the

mouse visual cortex, opening up a horizon for intravital imaging to understand the organizations and functions of biological systems at a holistic level.



Disclosures: **Z. Zhao:** None. **J. Wu:** None. **Q. Dai:** None.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.10/U11

Topic: I.03. Anatomical Methods

Support: Max Planck Society

Title: Connectomic screening of mouse models of autism

Authors: *A. KHALIFA, S. LOOMBA, V. GANGADHARAN, M. HELMSTAEDTER;
Max Planck Inst. For Brain Res., Frankfurt Am Main, Germany

Abstract: Autism spectrum disorder is highly heterogeneous, with hundreds of genes associated with its etiology. One leading hypothesis is that this heterogeneity converges onto a simpler circuit phenotype at the synaptic level. Imaging these wiring diagrams at synaptic resolution across large volumes has long been a challenge. In addition, it has been difficult to densely measure circuit elements to account for the broad effects of homeostatic mechanisms that balance neurodevelopmental perturbations. Furthermore, high precision and statistical power have been required to account for en-masse effects that act additively among many factors each with small contribution in the parameter space. We approached these problems by using volume electron microscopy, dense staining and computational methods. We applied forward connectomic screening to the cortical tissue of four genetic mouse models of autism (Shank3 KO, CNTNAP2 KO, Fmr1 KO and NLGR451c) which include both syndromic and nonsyndromic associated mutations, to study neuronal circuits at the synaptic level. We analyzed the balance of inhibition and excitation at the level of neurons, synaptic input to pyramidal and interneuron cells, and axonal output properties. A multinomial model was built to infer excitatory and inhibitory properties of anatomically identified synapses. We found a convergent effect on the I/E balance, represented differently in the circuit parameter space among the genetic models. Synapse-level alterations were found in both the excitatory and inhibitory subcircuits. Additional control analyses confirmed the model's predictions.

Disclosures: A. Khalifa: None. **S. Loomba:** None. **V. Gangadharan:** None. **M. Helmstaedter:** None.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.11/U12

Topic: I.03. Anatomical Methods

Title: Mapping Structural Organization in Neurobiology with MINFLUX Nanoscopy

Authors: J. WIRTH[1], M. VELASCO[1], C.-M. GÜRTH[2], O. BRUN[1], *J. MATTHIAS[1];
[1]Abberior Instruments America LLC, Bethesda, MD; [2]Abberior Instruments GmbH, Heidelberg, Germany

Abstract: According to the fundamental principle of the structure-function relationship, the intricate geometry of biomolecules and their assemblies directly governs their specific interplay. Thus, mapping the distribution of key player proteins in neurobiology with fluorescence microscopy will advance our understanding of neuronal processes, bringing us one step closer to unravelling the complexity of brain function. With dimensions smaller than the diffraction limit, specifically synapses and their dense protein population call for advanced super-resolution techniques. MINFLUX nanoscopy is paving the way towards the direct visualization of the structural organization of (macro)molecular complexes and their subcellular distribution. MINFLUX probes the positions of individual fluorophores with an excitation intensity minimum, providing the most photon-efficient concept of localizing single emitters [1,2]. MINFLUX combines single-digit nanometer localization precision with molecular specificity and live-cell compatibility on a standard light microscopy setup [3], allowing to easily implement this technique into common workflows in a wide range of neuroscience applications. We present MINFLUX as a versatile tool to map the 3D structural organization of protein populations in fixed and living neurons at molecular resolution (e.g. [4]). [1] Balzarotti et al. (2017), Nanometer resolution imaging and tracking of fluorescent molecules with minimal photon fluxes, *Science* **355** [2] Gwosch et al. (2020), MINFLUX nanoscopy delivers 3D multicolor nanometer resolution in cells, *Nat Methods* **17** [3] Schmidt et al. (2021), MINFLUX nanometer-scale 3D imaging and microsecond-range tracking on a common fluorescence microscope, *Nat Commun* **1** [4] Grabner et al. (2022), Resolving the molecular architecture of the photoreceptor active zone with 3D-MINFLUX, *Sci Adv* **8**

Disclosures: J. Wirth: A. Employment/Salary (full or part-time):; Abber. **M. Velasco:** A. Employment/Salary (full or part-time):; Abberior Instruments America LLC. **C. Gürth:** A. Employment/Salary (full or part-time):; Abberior Instruments GmbH. **O. Brun:** A. Employment/Salary (full or part-time):; Abberior Instruments America LLC. **J. Matthias:** A. Employment/Salary (full or part-time):; Abberior Instruments America LLC.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.12/U13

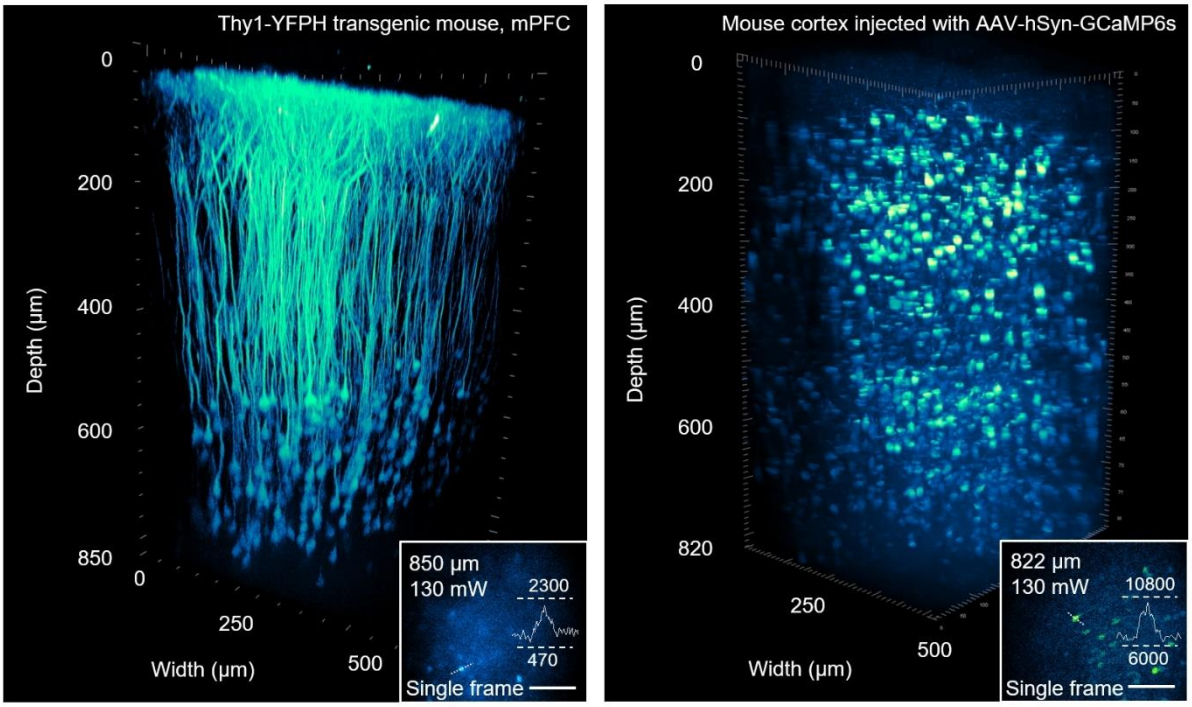
Topic: I.03. Anatomical Methods

Support: STI2030-Major Projects 2021ZD0202205
National Natural Science Foundation of China 8200907151

Title: Multicolor miniature microscopy for deep brain imaging with scalable field of view

Authors: *R. WU;
Beijing Information Sci. & Technol. Univ., Beijing, China

Abstract: Runlong Wu[1,2#]*, Chunzhu Zhao[1#], Yufei Zhu[1], Shan Qiu[1], Huaqiang Fang[3], Lifeng Zhang[3], Qiang Fu[4], Yanhui Hu4, Dong Zhang[1], Conghao Wang[5], Dakun Wu[7], Fei Yu[7] , Lishuang Feng[5], Yunfeng Zhang[1], Liangyi Chen[1], Heping Cheng[1]*, Aiming Wang[1]*
1 Peking University, China; 2 Beijing Information Science and Technology University, China; 3 PKU-Nanjing Institute of Translational Medicine, China; 4 Beijing Transcend Vivoscope Biotech Co., Ltd., China; 5 Beihang University, China; 6 University of Chinese Academy of Sciences, China; 7 Chinese Academy of Sciences, China. # R.W. and C.Z. contributed equally to this work. *****
Corresponding author E-mail: rlwu@bistu.edu.cn, chengp@pku.edu.cn, wangaimin@pku.edu.cn
Abstract: In the study of neural networks, it is crucial to image the structures and functions of different types of cells in the brain, from the superficial to the deep layers, in freely behaving animals. Here, we report on a 2.6 g multicolor miniature two-photon microscope (FHIRM-TPM 3.0). By designing broadband nested anti-resonant hollow-core fiber and fully correcting optical system chromatic aberration, we achieved multi-wavelength excitation imaging at 780 nm, 920 nm, and 1030 nm. By analyzing optimal excitation and collection numerical apertures, and combining this with spherical aberration correction design, we achieved structural and functional imaging of the cortex at depth up to 850 μm with resolution at dendritic spine level. Furthermore, through the use of three interchangeable objective lenses with different magnifications in a conjugate focusing design, we achieved scalable imaging across a 10-fold field of view, with a maximum field of view of 1×0.8 mm^2. We demonstrated the practicality of this microscope by performing multicolor simultaneous imaging of different types of neural cells on awake and freely moving mice.



Disclosures: R. Wu: None.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.13/U14

Topic: I.03. Anatomical Methods

Title: A Gentler Approach to STED Microscopy for Neuroscience Research

Authors: *M. VELASCO[1], N. T. URBAN[2], J. MATTHIAS[1], C. WURM[1];
[1]Abberior Instruments America LLC, Bethesda, MD; [2]Imaging Ctr., Max Planck Florida Inst. for Neurosci., Jupiter, FL

Abstract: STimulated Emission Depletion (STED) microscopy routinely enables the super-resolution imaging of nanoscale structures in (neuro)biology specimens [1, 2]. In traditional implementations of STED microscopy, resolution capabilities down to 20-30 nm are achievable, but often at the cost of fluorophore bleaching and toxicity to the sample [3, 4]. As a result, the resolution one can achieve when applying STED microscopy to sensitive samples such as neurons is often limited.
The challenge of photobleaching and phototoxicity can be addressed from two fronts. On the instrumentation side, using gentler imaging schemes [5, 6], collectively known as "Adaptive Illumination," can minimize the unnecessary exposure of the specimen to high intensity laser light. By adapting the intensity of the excitation and depletion lasers such that pixels containing structures of interest are probed as usual but "empty" pixels receive no illumination, one can preserve both fluorophore and specimen integrity without compromising the achievable resolution.
On the sample preparation front, novel labelling schemes such as Super-resolution Shadow Imaging (SUSHI) [7] and (STED-adapted) Point Accumulation for Imaging in Nanoscale Topography (PAINT) [8], can be used to achieve high signal-to-noise images despite photobleaching. In both these approaches, the presence of a "sea" of dye molecules is exploited to continuously replenish the fluorescent signal.
We will highlight how a two-pronged approach to alleviating photobleaching and phototoxicity is especially effective. We will demonstrate how the synergy of Adaptive Illumination and SUSHI and/or STED-PAINT can be utilized for gentler STED microscopy in a wide range of neurobiology specimens.
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[2] Tønnesen & Nägerl (2013), Superresolution imaging for neuroscience, *Exp. Neurol.* **242**
[3] Kilian et al. (2018), Assessing photodamage in live-cell STED microscopy, *Nat. Methods* **15**
[4] Oracz et al. (2017), Photobleaching in STED nanoscopy and its dependence on the photon flux applied for reversible silencing of the fluorophore, *Sci. Rep.* **7**
[5] Staudt et al. (2011). Far-field optical nanoscopy with reduced number of state transition cycles, *Opt. Express* **19**
[6] Heine et al. (2017), Adaptive-illumination STED nanoscopy, *Proc. Natl. Acad. Sci., S.* **114**
[7] Tønnesen et al. (2018), Super-resolution imaging of the extracellular space in living brain

tissue, *Cell* **172**
[8] Spahn et al. (2019) Protein-specific, multicolor and 3D STED imaging in cells with DNA-labeled antibodies, *Angew. Chem.* **131**

Disclosures: M. Velasco: A. Employment/Salary (full or part-time):; Abberior Instruments America LLC. **N.T. Urban:** A. Employment/Salary (full or part-time):; Max Planck Florida Institute for Neuroscience. **J. Matthias:** A. Employment/Salary (full or part-time):; Abberior Instruments America LLC. **C. Wurm:** A. Employment/Salary (full or part-time):; Abberior Instruments America LLC.

Poster

PSTR048: Light and Electron 3D Microscopy Methods

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.14/U15

Topic: I.03. Anatomical Methods

Title: Characterizing Whole Brain Neuronal Seizures in Live Zebrafish with Fourier Light Field Microscopy

Authors: *L. OJEDA[1], M. JONES[1], Y. BAI[1], S. E. FRASER[2], T. V. TRUONG[3];
[1]Biomed. Engin., [2]Mol. & Computat. Biol., [3]Translational Imaging Ctr., USC, Los Angeles, CA

Abstract: Epilepsy is the most common chronic brain disease, affecting over 50 million people globally, with 80% of cases occurring in low to middle-income countries. Epilepsy is characterized by spontaneous and synchronous neuronal hyperactivity commonly associated with recurrent twitches and seizure symptoms. Despite advances in seizure research, understanding the initiation and spread of runaway activation across all brain regions has been constrained by limitations in volumetric imaging methods. We developed a Fourier Light Field Microscopy (FLFM) platform for whole-brain functional imaging of live zebrafish larvae to study seizures. Zebrafish are a commonly used vertebrate model for research due to their rapid development, small size, and suitability for high-throughput behavioral assays. Their larvae's transparent, underdeveloped skulls also facilitate non-invasive whole-brain imaging. Light sheet microscopy is capable of whole-brain zebrafish imaging and reconstruction; however, the imaging depth (150 um) and speed (10 Hz) are limited due to the need to scan plane by plane. FLFM can image an extended 3D volume (250 um depth) in a single snapshot, generating a set of simultaneous multi-view projections that can be reconstructed to the original 3D sample. This allows for high-speed volumetric imaging acquisition (30+ Hz) to capture the fast and sudden neuronal activity of seizures across the full brain volume. We use a transgenic zebrafish line (HuC:GCaMP7f) that pan-neuronally expresses the calcium indicator for fluorescent neuronal activity visualization. Our zebrafish are paralyzed with bungarotoxin and immobilized in an agarose mold to prevent movement during imaging. Our initial efforts focus on a coarse-grained analysis of seizure events following 15 mM of pentylenetetrazol (PTZ) administration, a GABA-antagonist that induces seizure activity in zebrafish, to characterize the spatial-temporal initiation and

progression of seizure neuronal activity. Our preliminary results show robust neuronal activity stemming from various regions of the brain and traveling outwards from the point of initiation in a wave-like propagation. We have not observed any temperature dependence associated with specific seizure initiation and directionality. This work reports a whole-brain high-resolution analysis of neuronal seizures in zebrafish, allowing for a comprehensive characterization of seizure progression. We aim to quantify the 3D further to characterize the fluorescence activity magnitude, duration, and wave propagation speed across the whole brain.

Disclosures: L. Ojeda: None. **M. Jones:** None. **Y. Bai:** None. **S.E. Fraser:** None. **T.V. Truong:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.01/U16

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Gpnmb spatial signature in glioblastomas: insights from an 8-plex SignalStar^{tm}multiplex immunohistochemistry panel for neurological microenvironment profiling

Authors: *R. CLARY[1], T. GUIDO[1], S. PHANSE[1], D. PAPALEGIS[2], S. KLEIN[2], P. SAVICKAS[1];
[1]HistoWiz, New York, NY; [2]Cell Signaling Technol., Danvers, MA

Abstract: Glycoprotein Nonmetastatic Melanoma Protein B (GPNMB) overexpression in glioblastomas is associated with tumor progression and poor clinical outcomes. GPNMB has also been shown to promote an immunosuppressive tumor microenvironment, driving increased M2-polarization in macrophages and microglia, and reduced activation and proliferation of T cells. Although GPNMB is an emerging biomarker of interest in immuno-oncology spaces, there is a clear gap in knowledge around the spatial signature of GPNMB in relation to lesioned or diseased areas of tissues.
In this study, we developed and validated an 8-plex SignalStarTM multiplex immunohistochemistry (mIHC) panel from Cell Signaling Technology® (CST) containing oligo-conjugated antibodies for GPNMB, Iba1, CD68, CD206, Ki67, CD8a, Granzyme B, and Pan-Keratin. This panel was applied to interrogate the spatial signature of GPNMB in relation to other immune cell markers in healthy and diseased tissue. This panel uses a single antibody incubation step for up to 8 targets and a network of complementary oligos with fluorescent dyes to amplify 4 channels at a time for imaging, resulting in 2 rounds of signal amplification, each followed by imaging; images are then aligned post hoc. This results in several advantages over tyramide based sequential staining paradigms, mainly decreased staining time, no concerns about epitope masking since all antibodies are applied together, and 8 easily separable fluorescent channels without bleed through.
Ongoing work will apply the panel to healthy and diseased human brain tissue to test the spatial

signatures of microglial activation under pathophysiological conditions. High resolution whole-slide images will be analyzed using Visiopharm software to assist in automated quantification of marker co-expression as well as to evaluate the proximity of proliferating cytotoxic T cells (CD8+, Granzyme B+, Ki67+) and M2-polarized macrophages (CD68+, CD206+) in relation to diseased tissue.
Understanding the immune response in relation to GPNMB expression is vital for the advancement of glioblastoma treatments in the future. Continued research in this area will play an important role in the development of potential therapeutic and in improving patient outcomes.

Disclosures: R. Clary: A. Employment/Salary (full or part-time):; HistoWiz. **T. Guido:** A. Employment/Salary (full or part-time):; HistoWiz. **S. Phanse:** A. Employment/Salary (full or part-time):; HistoWiz. **D. Papalegis:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **S. Klein:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **P. Savickas:** A. Employment/Salary (full or part-time):; HistoWiz.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.02/U17

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Biophysical methodologies for the QC of Abcam rabbit monoclonal antibodies (RabMAb®) in the neuroscience field

Authors: *W. HOWAT[1], A. KARPATI[7], C. WICKRAMASINGHE[2], **D. MOORE LAI**[3], F. TOOKE[4], R. KUMARAN[5], J. AYTON[5], Y. XU[6];
[1]R&D, [2]Product portfolio, Abcam, Cambridge, United Kingdom; [3]R&D, Abcam, Waltham, MA; [4]Protein Develop., [5]Abcam, Cambridge, United Kingdom; [6]Abcam, Waltham, MA; [7]Abcam Inc., Cambridge, United Kingdom

Abstract: Abcam’s recombinant rabbit monoclonal antibodies and proteins are validated to the highest standard for use in the neuroscience field as well as discovery and research assays worldwide. In addition to the application tests expected by the neuroscientists to confirm specificity and sensitivity, we have supplemented these QC methods with biophysical methodologies of LC-MS and HPLC to measure identity, purity and aggregation. Utilizing these core biophysical processes, we have greater than 9,000 RUO recombinant rabbit monoclonal antibodies characterized to date. The addition of these QC methods provides additional confidence for the researcher in the quality of the products and provides a reliable and consistent measurement of production to provide reproducibility to our customers.

Disclosures: W. Howat: A. Employment/Salary (full or part-time):; Abcam, Danaher Life Sciences. **A. Karpati:** A. Employment/Salary (full or part-time):; Abcam, Danaher Life Sciences. **C. Wickramasinghe:** A. Employment/Salary (full or part-time):; Abcam, Danaher

Life Sciences. **D. Moore Lai:** A. Employment/Salary (full or part-time):; Abcam, Danaher Life Sciences. **F. Tooke:** A. Employment/Salary (full or part-time):; Abcam, Danaher Life Sciences. **R. Kumaran:** A. Employment/Salary (full or part-time):; Abcam, Danaher Life Sciences. **J. Ayton:** A. Employment/Salary (full or part-time):; Abcam, Danaher Life Sciences. **Y. Xu:** A. Employment/Salary (full or part-time):; Abcam, Danaher Life Sciences.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.03/U18

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NINDS Grant 1K08NS123552-01
Marie Sklodowska-Curie grant agreement no. 896725

Title: Arrayed CRISPR/Cas9 loss-of-function screen in neuronal model of adaptor protein complex 4 deficiency identifies modulators of ATG9A trafficking

Authors: *M. ZIEGLER[1,2], C. BÖGER[1], J. ALECU[1], A. SAFFARI[1], A. K. DAVIES[3], M. SAHIN[1], D. EBRAHIMI-FAKHARI[1];
[1]Dept. of Neurol., Boston Children's Hosp., Boston, MA; [2]Department of Functional Neuroanatomy, Heidelberg University, Heidelberg, Germany; [3]Dept. of Mol. and Cell. Function, Univ. of Manchester, Manchester, United Kingdom

Abstract: Adaptor protein complex 4 associated hereditary spastic paraplegia (AP-4-HSP) comprises four types of HSP sharing identical clinical and molecular phenotypes due to loss-of-function variants in one of the four AP-4 subunits. The absence of AP-4 results in mislocalization of several proteins including the autophagy related protein 9A (ATG9A) which accumulates in the trans-Golgi network (TGN). Leveraging this screenable cellular phenotype, we established a platform for an arrayed CRISPR/Cas9 loss-of-function screen using AP-4 deficient SH-SY5Y neuroblastoma cells as a neuronal model. Our screening platform demonstrated robust assay performance meeting predefined quality criteria for small molecule and siRNA screens. We aimed to identify genetic modifiers which upon inhibition reinstate ATG9A export from the TGN as potential targets for drug development in AP-4-HSP. Therefore, we applied the Synthego Druggable Genome Library comprising 8,478 genes arrayed in a 384 format, with each gene targeted using three different sgRNAs. Quantification of ATG9A accumulation in the TGN was conducted using high-content fluorescent imaging, coupled with an automated image analysis pipeline, enabling precise protein localization within distinct subcellular compartments. Subsequent rescreening of the top 150 genes led to the identification of 44 candidates significantly impacting ATG9A localization. For detailed characterization of involved pathways, we devised a customized pathway analysis integrating gene ontology and a pathway impact score, revealing 14 distinct pathway clusters. Predominant clusters implicated in AP-4 dependent protein trafficking included potassium channel activity, oxidative degradation,

and vesicular trafficking. Within each cluster, we also characterized key protein families, such as potassium channels, small GTPases and cytochrome P450 enzymes. Further validation corroborated the significance of selected genes, with alanyl aminopeptidase (ANPEP) emerging as particularly promising target whose inhibition effectively reversed ATG9A accumulation in AP-4 deficiency syndrome. In summary, our large-scale arrayed CRIPR/Cas9 loss-of-function screen underscores the potential of arrayed CRISPR screens for functional genomics. Through this approach, we delineated the modulatory landscape of ATG9A trafficking in AP-4 deficient neuronal cells and identified ANPEP as a potential druggable therapeutic target for AP-4-HSP.

Disclosures: M. Ziegler: Other; Bayer Foundation, German Academic Exchange Service, German National Academic Foundation. **C. Böger:** None. **J. Alecu:** None. **A. Saffari:** None. **A.K. Davies:** None. **M. Sahin:** None. **D. Ebrahimi-Fakhari:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.04/U19

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: F30DA057838-02 (LBE)
R01NS081071 (Mao)
RF1NS133599 (Mao,Zhong)
R01NS104944 (Zhong, Mao, Li)
RF1MH120119 (Zhong, Mao)
U01NS094247 (Zhong, Mao)

Title: Genetically-encoded fluorescence lifetime sensors for imaging of neuromodulation in vivo

Authors: *L. BAYLESS-EDWARDS, T. YAHIRO, J. A. JONES, T. MAO, H. ZHONG; Vollum Inst., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: The majority of neuromodulators bind to G-protein coupled receptors that signal through a biochemical cascade of intracellular small molecules and effectors such as cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), and protein kinase C (PKC). The neuron can integrate the signaling of multiple neuromodulators through their differential effects on these signaling pathways. Thus, examining the dynamics of these intracellular signals should reveal how neurons respond to and integrate information from multiple neuromodulators. Built upon our recent success of generating genetically-encoded sensors that can be used *in vivo* to examine Gi and Gs modulation of cAMP and PKA, we sought to establish *in vivo* monitoring of PKC which signals through the Gq pathway. Here, we present CKAR3, a sensor for PKC activity that is compatible with *in vivo* fluorescence lifetime imaging. We have carried out extensive characterization of CKAR3 *in vitro* and *in vivo* and found that CKAR3 has a 10-fold increased dynamic range compared to previous sensors. It also reveals PKC activity modulation in

response to pharmacological and behavioral manipulation *in vivo*. The use of this sensor *in vivo* will allow us to examine the role of PKC in neuronal function and interrogate the neuromodulators that govern its activity.

Disclosures: L. Bayless-Edwards: None. **T. Yahiro:** None. **J.A. Jones:** None. **T. Mao:** None. **H. Zhong:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.05/U20

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: the Japan Society for the Promotion of Science

Title: Scaffold-free Bio 3D conduits derived from human dental pulp stem cells promote peripheral nerve regeneration

Authors: *Y. KAWASE-KOGA[1,2], Y. CHUJO[2,1], A. HATORI[3], M. NAKANO[1], Y. KANNO[1,2], T. AOYAMA[4], R. IKEGUCHI[5], Y. MIYAZAKI[6], Y. TORII[6], S. AKIEDA[6]; [1]Div. of Maxillofacial Surgery and Stomatology, Dept. of Oral and Maxillofacial Surgery, Tokyo Women's Med. Univ., Tokyo, Japan; [2]Dept. of Oral and Maxillofacial Surgery, Tokyo Med. Univ., Tokyo, Japan; [3]Dept. of Endodontology, Sch. of Dent. Medicine,, Univ. of Connecticut Hlth., Connecticut, CT; [4]Dept. of Physical Therapy, Human Hlth. Sciences, Grad. Sch. of Medicine,, [5]Dept. of Orthopedic Surgery and Rehabil. Medicine, Grad. Sch. of Med., Kyoto Univ., Kyoto, Japan; [6]Cyfuse Biomed. K.K., Tokyo, Japan

Abstract: Objective: Peripheral neuropathy in the maxillofacial region significantly reduces the quality of life of patients due to functional and aesthetic deficits. Currently, autologous nerve transplantation is the gold standard treatment of peripheral nerve injuries, however the invasiveness of the donor site remains an issue. Although artificial nerves have been developed in recent years, the results have not exceeded those of autologous nerve transplantation. On the other hand, a technique to fabricate 3D structures composed only of cells without using scaffold materials by layering cell aggregates (spheroids) using a Bio 3D printer has been attracting attention. In this study, we developed 3D structures using human dental pulp stem cells (hDPSCs) and Bio-3D printing technology, and investigated its nerve regeneration ability by transplanting it into a rat sciatic nerve injury model. **Materials & Methods:** hDPSCs were isolated and cultured from a patient's extracted tooth to form spheroids, which were then layered using a Bio-3D printer to create scaffold-free Bio 3D conduits. Male rats with immune deficiency underwent mid-thigh-level transection of the right sciatic nerve. The 8-mm Bio 3D conduit was transplanted into 5-mm defect of the right sciatic nerve. Eight weeks after transplantation, a walking test and Toe-Spread test were performed to evaluate the function of sciatic nerve regeneration. Histological evaluation was also performed by HE staining and

toluidine blue staining. **Results:** The Bio 3D group showed functional differences in a walking test and Toe-Spread test compared to the control group. Myelinated axons were also observed in tissue sections of the Bio 3D group. **Conclusions**: This study suggests the efficacy of sciatic nerve regeneration using 3D structures composed only of cells by hDPSCs with Bio-3D printer technology. We plan to conduct a validation study of nerve regeneration in the maxillofacial region.

Disclosures: Y. Kawase-Koga: None. **Y. Chujo:** None. **A. Hatori:** None. **M. Nakano:** None. **Y. Kanno:** None. **T. Aoyama:** None. **R. Ikeguchi:** None. **Y. Miyazaki:** None. **Y. Torii:** None. **S. Akieda:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.06/U21

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Samsung Grant SSTF-BA2102-09

Title: Development active enhancer based stimulus specific reporter system

Authors: *H. KIM, N. JUNG, M. SIM, T.-K. KIM;
Pohang Univ. of Sci. and Technol., Pohang/Gyeongsangbuk-do, Korea, Republic of

Abstract: Neuronal activity-based reporters, such as population calcium imaging and immediate early genes (IEGs)-based mapping, have revolutionized our understanding of the functional organization of neuronal circuits and how the brain processes sensory information to encode behaviors. Although powerful, currently available activity reporters primarily reflect general neuronal activity, lacking the capacity to offer region- and/or stimulus-specific information. To address this limitation, we are developing the Enhancer-Specific Neuronal Activity REporter (ENSNARE), which utilizes enhancers activated in response to specific sensory information across various brain regions. Using Chromatin Run-On sequencing (ChRO-seq), we analyzed the differential expression patterns of enhancer RNA (eRNA), a marker of functionally active enhancers. We identified 47 cocaine-specific eRNAs in the dorsal striatum (DS). This method facilitated the creation of a Cre-dependent reporter system that specifically identifies neurons activated by cocaine in the DS region of the mouse brain. Interestingly, ENSNARE identified a unique subset of neurons distinct from those detected by the Fos-based reporter (FosTRAP), yet manipulating their activity with Designer Receptors Exclusively Activated by Designer Drugs (DREADD) led to alteration in addiction-related behaviors, such as cocaine-induced locomotor sensitization (N=10, Cocaine 25mg/kg, CNO 10mg/kg) and conditioned place preference (CPP) (N=12, Cocaine 25mg/kg, CNO 10mg/kg). These findings indicate that current activity marking systems may not fully capture the complete neuronal ensemble involved in specific behaviors.

Out study also underscores the potential of the ENSNARE system as a versatile tool for unraveling the complex molecular intricacies of the brain.

Disclosures: H. Kim: None. **N. Jung:** None. **M. Sim:** None. **T. Kim:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.07/Web Only

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: R01MH125979

Title: Optimization of lipid nanoparticle delivery of gene-editing tools in the mouse brain

Authors: *R. A. GONZALES-ROJAS[1], S.-J. KANG[1], Y.-J. CHEN[1], H. HAN[2], N. MURTHY[2], H. LEE[1];
[1]Cell. and Integrative Physiol., Univ. of Texas Hlth. Sci. Ctr. at San Antonio, San Antonio, TX; [2]Dept. of Bioengineering, Univ. of California, Berkeley, Berkeley, CA

Abstract: Non-viral gene delivery vehicles possess tremendous advantages over traditional viral vectors in terms of biocompatibility and carrying capacity. However, non-viral vectors exhibit lower editing efficiency compared to viral vectors, particularly in the central nervous system. Among non-viral vectors, lipid nanoparticles (LNPs) delivering mRNAs have proven their biocompatibility through wide testing in COVID-19 vaccines. Although mRNA-based therapies may offer recourse for neurological conditions lacking effective treatments, the optimal delivery system of Cas9 mRNA and its sgRNA remains unclear. Here, we examined various modifications to a standard LNP (DLin-MC3-DMA) to increase its editing efficiency in the brains of Ai9 adult mice. First, we examined how introducing an acid-degradable aspect to PEGylated lipids improves LNP editing efficiency. Second, we determined the optimal injection rate and volume for minimal reflux in a brain tissue analog. Third, we are exploring how the ratio of Cas9 mRNA to sgRNA impacts editing efficiency in the mouse hippocampus. We hope that our delivery system is suitable for pathophysiological gene targets in mouse models for neurological disorders.

Disclosures: R.A. Gonzales-Rojas: None. **S. Kang:** None. **Y. Chen:** None. **H. Han:** None. **N. Murthy:** None. **H. Lee:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.08/U22

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: TSGH_B_113026
TSGH_E_113252
TSGH_B_113023

Title: Transplantation of the neural progenitor cell-engineered cell sheet promotes in situ neurovascular tissue repair and functional improvement in a rat model of surgical brain injury

Authors: *C.-H. CHOU[1], Y. LI[2];
[1]Tri-Service Gen. Hosp., Natl. Def. Med. Ctr., Taiwan, Taipei City, Taiwan, Taiwan; [2]Dept. of Pathology, Tri-Service Gen. Hosp., Natl. Def. Med. Ctr., Taipei City, Taiwan

Abstract: Brain injuries cause neurological damage that usually cannot fully recover. Stroke and neurodegenerative diseases, which all involve loss of brain tissue, are global health problems that are becoming increasingly serious in aging societies. Therefore, reconstruction of lost brain tissue is an important task in the field of tissue engineering, and brain tissue regeneration and neurological function recovery are the main goals of advanced clinical and neuroscience research. We first designed a novel co-culture model using human brain neural progenitor cells (hNPCs) and human cerebral microvascular endothelial cells (hCMECs) to form the NPC-engineered cell sheet (NECS) for rebuilding cerebral neurovascular tissue. The hCMECs provide the required growth factors and extracellular matrix, inducing hNPCs to differentiate into neurons, astrocytes and oligodendrocytes, while the hCMEC layer is induced by hNPCs to form vascular branches, effectively supplying hNPCs nutrients. To investigate how NECS affects microglial polarization, a triple culture model was created using the Transwell assay. An ongoing transcriptome analysis and single-cell RNA-seq is employed to identify the role of each cell type within the NECS. In the preclinical animal efficacy verification, we used a rat model of surgical brain injury (SBI) and conducted NECS transplantation. Neurobehavioral assessments revealed that rats in the treatment group performed significantly better than those in the control group. The modified neurological severity score (the most severe group, 18 points, the normal group, 0 points) was used for functional evaluation. Four weeks after NECS transplantation, the average score of the treatment group was 2 points, which was significantly better than the average score of 7 points in the control group. We further demonstrated that NECS transplantation yielded in situ neurogenesis and angiogenesis, and the unique pattern of host brain cells migrating into the NECS by CLARITY (*C*lear *L*ipid-exchanged *A*crylamide-hybridised *R*igid *I*maging/Immunostaining/In situ-hybridisation-compatible *T*issue-h*Y*drogel) and immunostaining. Taken together, NECS transplantation promotes in situ neurovascular tissue repair and functional recovery following SBI by mediating microglia activation and providing extracellular matrix essential for tissue reconstruction. hNPCs and hCMECs contribute to brain tissue regeneration via spatially and temporally reciprocal relationships including intercellular and cell-matrix interactions.

Disclosures: C. Chou: None. **Y. li:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.09/U23

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: In vitro development neurotoxicity (DNT) assay using CYTOQUBE and FDSS

Authors: N. NAGAFUKU[1], R. YOKOI[1], N. MATSUDA[1], Y. ISHIBASHI[1], **Y. WANG**[2], S. HISADA[3], H. HORAI[3], *I. SUZUKI[1];
[1]VitroVo, inc., Sendai, Miyagi, Japan; [2]Hamamatsu Corp., Edison, NJ; [3]Hamamatsu Photonics K.K., Hamamatsu, Japan

Abstract: Developmental Neurotoxicity (DNT) caused by chemical substances has become a pressing issue that needs to be addressed. Last year, the OECD published initial recommendations on evaluation of data from the DNT in vitro testing batter. The fundamental neurodevelopmental processes include the proliferation of progenitor cells, apoptosis, migration, neuronal differentiation, neurite outgrowth, neurite maturation and synaptogenesis, glial differentiation, and the neural network formation. 17 assays have been proposed to assess these processes. Assays evaluating proliferation, migration, neuronal differentiation, neurite outgrowth, and glial differentiation have been proposed using NPC-based 3D neurospheres. In this study, we utilized Cyte Cube (Hamamatsu Photonics K.K.), a microplate cytometer capable of high-speed fluorescence measurements and imaging for 3D cellular samples, to assess NPCs across different developmental stages. Furthermore, while the Neuronal Network Formation assay currently relies on micro-electrode array (MEA) technology, a Ca2+ transient assay can facilitate high-throughput functional measurements. Using FDSS/µCELL(Hamamatsu Photonics K.K.), we detected dose-dependent neurotoxic risk from pesticide-related compounds through Ca2+ transients. Subsequently, using the same samples, we evaluated neurite maturation and synaptogenesis with Cyte Cube, demonstrating that multiple DNT assays can be performed simultaneously on a single sample. These assays with Cyte Cube and FDSS/µCELL have proven to be effective for DNT assays utilizing 3D neurospheres.

Disclosures: **N. Nagafuku:** None. **R. Yokoi:** None. **N. Matsuda:** None. **Y. Ishibashi:** None. **Y. Wang:** None. **S. Hisada:** None. **H. Horai:** None. **I. Suzuki:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.10/Web Only

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: https://doi.org/10.54499/PTDC/BTM-ORG/0055/2021
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Title: Gender-related metabolic insights and cryopreservation validation in urine-derived stem cells from healthy human donors

Authors: G. J. AFONSO[1], C. CAVALEIRO[1], P. J. OLIVEIRA[2,3], J. VALERO[4], S. I. MOTA[2,3], ***E. FERREIRO**[2,3];
[1]Ctr. for Neurosci. and Cell Biol., Univ. of Coimbra, Ctr. for Innovative Biomedicine and Biotech., Univ. of Coimbra, Coimbra, Portugal; [2]Ctr. for Neurosci. and Cell Biol., Univ. of Coimbra, Coimbra, Portugal; [3]Centre for Innovative Biomedicine and Biotechnology, University of Coimbra, Coimbra, Portugal; [4]Cell Biol. and Pathology, Inst. of Neurosci. of Castilla y León. Univ. of Salamanca., Salamanca, Spain

Abstract: *Introduction: Urine is increasingly recognized as a valuable and non-invasive source of human stem cells, making it ideal for personalized medicine. However, our knowledge of urine-derived stem cells is still evolving, with gaps at the understanding of gender-related specificities due to inherent biological differences. Additionally, being primary cells with variable colony formation timeframes and proliferation rates, coordinating experiments may be challenging without a validated long-term cryopreservation method.*
Objectives: To advance the characterization of these cells, our first objective was to metabolically profile them and discern differences between male and female donors. The second goal was to validate a cryopreservation protocol, comparing various metabolic parameters and cell viability between fresh and thawed cells.
Methods: Urine-derived stem cells were isolated from healthy individuals' urine (26-50 years old) and cultured in 1:1 DMEM+KSFM media. At passages 2-4, a portion was cryopreserved in the mentioned media supplemented with 5% DMSO. Fresh and thawed cells underwent flow cytometry for apoptosis/necrosis identification and cell viability assays using resazurin and sulforhodamine B. Metabolic characterization was carried out through Seahorse Mito Stress and Glycolysis Stress assays.
Results: No significant differences were observed regarding the investigated time-points among cell groups and genders. Cryopreserved and fresh cells exhibited similar viability and showed no alterations in cell respiration and glycolysis-associated parameters.
Conclusion: The absence of noticeable differences between males and females in the observed parameters supports the use of this cellular model irrespective of gender-specificities, at least under our conditions and at this age interval. The validated cryopreservation protocol opens new avenues for planning experiments using this model.
Funding: Work financed by ERDF under the project 0145_CROSS_3DTOOL_4ALS_3_P, through the COMPETE2020 - Operational Programme for Competitiveness and Internationalization, and Portuguese national funds via FCT (https://doi.org/10.54499/PTDC/BTM-ORG/0055/2021, UIDB/04539/2020, UIDP/04539/2020,

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Disclosures: G.J. Afonso: None. **C. Cavaleiro:** None. **P.J. Oliveira:** None. **J. Valero:** None. **S.I. Mota:** None. **E. Ferreiro:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.11/U24

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Novel Gold Nanoparticles for Brain Cancer Diagnostics using CT Imaging

Authors: *P. RAMAKRISHNA[1,2], O. A. SHEMESH[1,2,3];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Neurobiology, University of Pittsburgh, Pittsburgh, PA; [3]Bioengineering, University of Pittsburgh, Pittsburgh, PA

Abstract: Precise, non-invasive diagnostics of cancer has been notoriously difficult, particularly for brain tumors. With a high spatial resolution and quick scan times, computed tomography (CT) is often used for acquiring scans with the greatest detail and expediency in preclinical and clinical settings. Despite these benefits, CT imaging suffers from a low signal-to-noise ratio because of the low contrast between tissues in the human body. CT contrast agents, such as Iodine, are often used to alleviate this downside but their usage for cancer imaging is extremely limited in scope due to low uptake in tissues and toxicity associated with higher doses. Gold nanoparticles (NPs) have recently emerged as a potential CT contrast agent due to their high x-ray attenuation, biocompatibility, and favorable surface chemistry. Currently, CT Imaging using gold NPs involves chemically synthesized gold NPs conjugated to various biomolecules and tissue specific antibodies for safe, tissue-specific labeling. However, this strategy brings with it several downsides stemming from inefficient antibody targeting, high systemic clearance and immunogenicity. To address these issues, we have developed a novel peptide-mediated labeling of tumors with gold NPs for enhanced detection using CT Imaging. This strategy achieves a significantly better delivery and targeting of gold NPs to cancerous tissues. As a result, the high-resolution-high-speed capabilities of CT Imaging can be readily taken advantage of for preclinical and clinical diagnosis of brain cancers such as gliomas, meningiomas, and astrocytomas.

Disclosures: P. Ramakrishna: None. **O.A. Shemesh:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.12/U25

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Differential co-expression analysis of spatial transcriptomics data to uncover novel biomarkers at the device-tissue interface

Authors: *B. GUPTA[1], A. SAXENA[2], M. G. MOORE[2], E. K. PURCELL[3];
[1]Neurosci. Program, Michigan State Univ., East Lansing, MI; [2]Biomed. Engin., Michigan State Univ., East Lansing, MI; [3]Biomed. Engin. & Neurosci. Program, Michigan State Univ., East Lansing, MI

Abstract: Implanted electrodes in the brain suffer from the longstanding obstacles of instable performance and poor tissue integration. The biological response to implanted electrodes is a well-known contributor to the challenge of obtaining a consistent and lasting device-tissue interface. Understanding this phenomenon on a cellular and molecular level could uncover information regarding recording signal instability and loss, off-target effects of neuromodulation, variability in stimulation thresholds and stimulation-induced loss in neural activity. Histological analysis of the tissue response post implantation is relatively limited and low-throughput involving the pre-selection of only a few markers of interest. Novel techniques of spatial transcriptomics allow for large scale mapping (whole transcriptome) of transcriptional changes with improved spatial resolution at the device-tissue interface alongside traditional immunohistochemistry. The data produced from profiling gene expression using spatial transcriptomics can further reveal information about the cellular and molecular changes taking place at and around the implanted site. In this work, we extend our experimental spatial transcriptomics findings by employing computational network analysis to identify biomarkers of interest at the device-tissue interface. Spatial transcriptomics data was collected from rats (n = 3) implanted with single shank, silicon, “Michigan”-style electrodes in the motor cortex for 1 day, 1 week or 6 weeks. Unimplanted tissue at each time point was used as controls. Differential co-expression analysis will reveal gene modules of interest by identifying changes in the correlation structure of counts of specific genes between samples of two different conditions, for example, implanted vs unimplanted tissue, and “near” device tissue vs “far” device tissue (i.e. distance from the device). Overall, this analysis will reveal new clusters of genes that could serve as novel biomarkers of the device-electrode interaction. The results from this work add to the growing body of literature suggesting intricate cellular and molecular changes taking place around implanted electrodes in the brain.

Disclosures: B. Gupta: None. **A. Saxena:** None. **M.G. Moore:** None. **E.K. Purcell:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.13/U26

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NS133364

Title: Using Machine Learning to Prioritize Cell-type-specific Enhancers of the Spinal Cord

Authors: M. LEONE[1], B. N. PHAN[2], H. SESTILI[1], B. LOPES[3], R. P. SEAL[4], A. R. PFENNING[5];
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Computat. Biol., Carnegie Mellon Univ., Pittsburgh, PA; [3]Univ. of Pittsburgh, Pittsburgh, PA; [4]Neurobio., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [5]Computat. Biol. Dept., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Chronic pain is a common and debilitating medical disease, and existing treatment options show limited effectiveness and have off-target effects. One potential gene therapy approach to treating pain is to deliver and activate exogenous transgenes in specific neurons of the dorsal horn, to inhibit chronic pain signals without impacting other functions such as motor, autonomic, and non-nociceptive sensation. It has been shown that enhancers can drive transgene expression with high cell-type specificity *in vivo*. However, systematic screening of candidate enhancers is resource- and time-intensive with a low success rate. To better prioritize candidates for screening, my lab developed the SNAIL approach (specific nuclear-anchored independent labeling). SNAIL uses an ensemble of convolutional neural networks (CNNs) trained on open chromatin data to prioritize the cell type-specificity of candidate enhancers. In this work, we develop SNAIL for the spinal cord based on a cross-species atlas of single-nucleus open chromatin data. First, by labeling single-nucleus open chromatin using single-nucleus RNA integration, we labeled 18 (15) neuron subtypes of the dorsal horn in macaque (mouse) datasets. Then for the 15 subtypes for which we had reliable cross-species open chromatin data, we trained CNNs to predict whether an open chromatin peak was specific to a cell type of interest versus other excitatory, inhibitory, ventral, or glial cells. We required at least 500 peaks per species and 2000 total peaks to train a model, while the majority of models had > 10000 peaks. All models exceeded an auROC of 0.84 and auPRC of 0.82, while the highest performing model was for the Neuropeptide Y (NPY) interneuron versus glial cells (auROC: 0.95, auPRC: 0.96). Models perform well at classifying both mouse and macaque-derived peaks (average mouse F1 score: 0.79, macaque F1 score: 0.83). Using our models, we ranked candidates to prioritize for further experimental validation, which is now in progress. Surprisingly, one candidate when paired with a synthetic transgene that inhibits neural activity (Designer Receptor Exclusively Activated by Designer Drugs) shows preliminary effects of blocking mechanical allodynia in a rodent model (N= 9 mice per condition, balanced males and female. Punctate allodynia $p<0.001$ and dynamic allodynia $p<0.05$). Further validation is needed to precisely establish the cell type(s) driven by this enhancer, its effects on phenotype, and its overall clinical potential.

Disclosures: M. Leone: None. **B.N. Phan:** None. **H. Sestili:** None. **B. Lopes:** None. **R.P. Seal:** None. **A.R. Pfenning:** A. Employment/Salary (full or part-time):; SNAIL Biosciences. F. Consulting Fees (e.g., advisory boards); Avista Therapeutics.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.14/U27

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Human AAV project with temporal lobectomy samples

Authors: *M. M. MORKAS[1], J. MCGINNIS[2], M. GUEVARA[2], S. MALLANNAGARI[4], B. R. ARENKIEL[3];
[1]Rice University/Baylor Col. of Med., Houston, TX; [3]Mol. & Human Genetis and Neurosci., [2]Baylor Col. of Med., Houston, TX; [4]Rice Univ., Houston, TX

Abstract: Adeno-associated viruses (AAVs) are the most widely used vectors in ongoing central nervous system gene therapy trials where genetic sequences are delivered into cells of interest; successful transduction of a specific cell type depends on the AAV's capsid. Although in the past, efforts to generate AAV capsids specific to cell types have been made, these efforts have been limited to animal models, primarily mouse; these models have seen low transferable validity across species and even between strains. To address this issue, we have adapted the human brain organotypic slice culture model, using living human brain tissue taken out during the course of routine brain surgeries (including from temporal lobectomies). We apply virus to the slices the day after collection, and maintain the tissue up until two weeks. Using immunohistochemistry and single nuclei sequencing, we determine different AAVs' abilities to transduce cells found in the temporal lobectomy samples. From our research, we found that temporal lobectomy samples can offer insight into the different cell types found in the temporal cortex and a means of screening cell-type specificity among AAV gene therapy vectors. Furthermore, we find that the samples are generally stable across 14 days in culture, and not substantially changed by the addition of virus. DJ8, AAV2-retro, and PHP.s display the greatest consistent transduction of neurons. In conclusion, this model is an ideal one to screen large new libraries of AAV variants for candidates that show cell-type specificity.

Disclosures: M.M. Morkas: None. **J. McGinnis:** None. **M. Guevara:** None. **S. Mallannagari:** None. **B.R. Arenkiel:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.15/U28

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Hacettepe Sientific Research Projects Support Unit-TOA-2023-20338

Title: Exploring mechano sensitive gene expression using a membrane based cell stretching devise

Authors: *P. DINÇER[1], N. DÜZ[2], I. UYANIK[3];
[1]Hacettepe Univ. Fac. of Med., Ankara, Turkey; [2]Med. Biol., Hacettepe University: Hacettepe Universitesi, Ankara, Turkey; [3]Electrical and Electronics Engin., Hacettepe Univ., Ankara, Turkey

Abstract: Mechanical stimuli, encompassing stretching, shear stress, and pressure, exert profound effects on extracellular functions by initiating mechanotransduction pathways and modulating gene and protein expression. This leads to cellular responses in function or phenotype. Mechanotransduction processes are integral to various cellular aspects, such as growth, development, differentiation, and intercellular interactions, and play a crucial role in maintaining tissue homeostasis in tissues relevant to neuroscience, including skeletal muscles, cardiac muscles, bones, cartilage, and blood vessels. Disruptions in mechanotransduction mechanics often lead to disturbances in organismal equilibrium.
In this study, we have engineered a membrane-based cell stretching device capable of applying uniaxial or biaxial mechanical stress on cells through sinusoidally-varying stretch at different magnitudes (5-20%), frequencies (0.2-2 Hz), and patterns. The functionality of this system was evaluated using q-PCR analysis of mechanosensitive genes (CTGF, C-MYC, MYL9), revealing upregulation of MYL9 and CTGF gene expression.
This innovative device serves as a powerful tool for exploring the effects of mechanical stress on cells within the realm of neuroscience research. Its versatility across various cell types and tissues offers promise for advancing our understanding of disease pathophysiology, elucidating regenerative mechanisms following neural tissue injury, and identifying potential pharmaceutical interventions in neuroscience. This study was supported by Hacettepe Sientific Research Projects Support Unit-TOA-2023-20338.

Disclosures: **P. Dinçer:** None. **N. düz:** None. **I. Uyanik:** None.

Poster

PSTR049: Gene, Protein, or Cell Based Approaches

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.16/U29

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Hacettepe Sientific Research Projects Support Unit-TOA-2023-20338.

Title: Polydimethylsiloxane membrane design for tissue engineering

Authors: *N. DÜZ[1], I. UYANIK[2], P. DINÇER[3];
[1]Hacettepe University: Hacettepe Universitesi, Ankara, Turkey; [2]Electrical and Electronics Engin., Hacettepe Univ., Ankara, Turkey; [3]hacettepe Univ., Ankara, Turkey

Abstract: Developing novel techniques for tissue engineering in skeletal muscle is essential for reconstructing muscle lost or damaged due to traumatic injuries or neuromuscular disorders such as muscular dystrophies. Cell stretching is a fundamental method used to investigate cell behavior under mechanical stresses. The reliability of these tests is critical and largely depends on membrane geometry and loading conditions. In this study, we designed and fabricated a polydimethylsiloxane (PDMS) membrane that exhibits a more uniform strain distribution and enhanced durability compared to commercially available membranes. Shape optimization, based on finite element analysis, was utilized along with adjustments to material properties to achieve the desired membrane performance. The biocompatibility of the fabricated PDMS membranes and the effects of synthesis conditions on cell response were evaluated. The results demonstrated the suitability of the membranes for in vitro applications using human myoblast cell lines. Cell adhesion, proliferation, and differentiation rates were found to be comparable to those of the control group. This study contributes to the development of innovative biomaterials suitable for cultivating skeletal muscle cells. This study was supported by Hacettepe Sientific Research Projects Support Unit-TOA-2023-20338.

Disclosures: **N. düz:** None. **I. Uyanik:** None. **P. Dinçer:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.01/U30

Topic: I.07. Data Analysis and Statistics

Title: Decoding Electrical Signals Between Neurons: An Approach to Analyze Voltages from Neuronal Firing

Authors: *C. ADAM[1], J. MARTINEZ[2], S. MUFTI[3], E. A. ROGERS[3], N. KRISHNAN[1], T. B. BEAUCLAIR[4], R. SHI[5];
[1]Purdue Univ., West Lafayette, IN; [2]Ctr. for Paralysis Res., Purdue Univ., West Lafayette, IN 47907., Lafayette, IN; [3]Biomed. Engin., Purdue Univ., West Lafayette, IN; [4]Purdue Univ., Lafayette, IN; [5]Depat. Basic Med. Sci., Purdue Univ., West Lafayette, IN

Abstract: Neuron signaling is crucial to health and involves voltage spikes that propagate through and between cells. Drugs or conditions (i.e. injury) can alter signal transmission. Quantifying how neurons signal could improve understanding, treatment, and early detection of diseases. However, such analysis is often purely qualitative, time consuming, or examines only correlations, thereby limiting information gained. For example, crosscorrelation, a standard (since the 1980s) analysis based on relative spike timings, involves creating a histogram called a correlogram whose shape contains information about the relationship between two signals. Ideally, a correlogram should be created for each pair of signals and correlogram shape properties quantified. However, most correlogram analyses are done manually, meaning results are rarely quantitative, and only a subset of relationships in a population are analyzed because

full analysis is too time consuming. To overcome this limitation, we developed an algorithm to analyze voltages from neuronal populations with minimal user effort. The algorithm outputs statistics on: (i) the number of times each signal spiked, (ii) intervals between spikes, (iii) and relationships between cells based on correlograms. Specifically (iii), the algorithm: tests for independent signals by testing for uniform distributions (Kolmogorov-Smirnov test, if $p<0.05$, two signals are not independent), determines whether one signal follows/leads another by calculating correlogram area left of zero (0.5 for simultaneous firing, < 0.5 for followers, > 0.5 for leaders), and quantifies firing patterns by counting the number of correlogram peaks, then outputs statistics for each metric. The algorithm was applied to microelectrode array recordings of voltage signals from cells given Bicuculline, a drug that synchronizes firing and simulates seizures *in vitro.* The uniformity metric captured synchronization (loss of independent relationships) caused by bicuculline. The peak count metric showed that the number of correlogram peaks decreases after bicuculline, suggesting firing patterns are less diverse after the drug. The area left of zero metric showed that bicuculline increases the number of cells that consistently fire before or after others, identifying potential pacemaker cells. In the future, this algorithm could be employed to analyze signals from neuronal populations subjected to other treatments or conditions such as neurodegeneration or injury to better understand neuronal communication and gain insight into disease treatment, detection, and management.

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Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.02/U31

Topic: I.07. Data Analysis and Statistics

Support: NIMH R01MH126236
NIA R01AG055544

Title: The spike dynamics and cross-correlation with local field potentials during medial entorhinal cortex inactivation

Authors: *B. ZHAO[1], Y. QIN[2], S. D. LOVETT[3], C. BESOSA[3], J. P. KENNEDY[3], S. N. BURKE[3], A. P. MAURER[4];
[1]Univ. of Florida Dept. of Neurosci., Gainesville, FL; [2]Civil & Coastal Eng., Univ. of Florida, Gainesville, FL; [3]Neurosci., Univ. of Florida, Gainesville, FL; [4]Evelyn F. McKnight Brain Inst., Univ. of Florida, Gainesville, FL

Abstract: Understanding the intricate dynamics of neural spikes and their interplay with local field potentials is pivotal for deciphering neural connectivity and underlying structures. Drawing upon the rich dataset generously shared by Zutshi and colleagues in 2022 (PMID: 34890566), we

study the firing rate patterns of both interneurons and pyramidal cells within the medial entorhinal cortex (mEC) during inactivation. We examined the interspike interval (ISI) distributions and ISI return maps for these cell types, capturing their activities under both the control condition and mEC inactivation. Through comparative analysis of ISI distributions between actively firing cells and those exhibiting reduced activity during inactivation, we unveiled differential impacts, with active cells experiencing lesser disruption compared to their less active counterparts. Extending our investigation to the CA1 inactivation, we observed a higher incidence of pyramidal cell suppression and particularly affected less active cells. Moreover, our exploration into the cross-correlation between spike multiunit activity (MUA) and theta waves uncovered a distinctive preferred delay, notably influenced by running speeds. These findings extend to theta-spike phase relationships and the effects of inactivation on place field dynamics, offering insights into the broader influences of neural activity modulation.

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Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.03/U32

Topic: I.07. Data Analysis and Statistics

Title: Discovering optimal information and temporal patterns of neural dynamics with hyperdimensional computing

Authors: *T. SAMIEI[1], E. NOZARI[2];
[1]Univ. of California, Riverside, Riverside, CA; [2]Mechanical Engin., Univ. of California, Riverside, Riverside, CA

Abstract: Decoding neural activity with optimal information and spatiotemporal resolution is critical for enhancing the efficiency of brain-computer interfaces in accuracy and timing. Significant research has pursued this aim by studying spatiotemporal patterns of information encoding and optimal decoding algorithms in neural data. In prior work, we developed a hyperdimensional computing framework to find the optimal extent of spatiotemporal aggregation for decoding static visual stimuli from multi-unit activity data recorded from mice. We introduced a theory of neural information processing, emphasizing dynamic variations in the unit of information based on neuronal signal and noise correlations across space and time. However, the encoding structure lacked flexibility in our previous approach, varying temporal resolution only via rigid bin sizes with equal weights and presumed correlations between adjacent time bins.
In this study, we aim to enhance the flexibility of encoding MUA data by introducing a more data-driven architecture to improve decoding accuracy and understand temporal and hierarchical aspects of information encoding in population-level spiking activity. Unlike previous

approaches, we devised a method to assign varying coefficients to different time bins based on their importance in the decoding process. By treating this as an optimization problem, we adjusted coefficients to prioritize informative time intervals, serving as a proxy for the amount of task-relevant information in data.
For mice viewing static images, our results indicate minimal encoding of information across the brain during the first 50ms post stimulus onset, evidenced by near-zero magnitude of optimal bin coefficients. Starting from 50ms after stimulus onset, we observe a rapid increase in information content, reaching its peak within the 50-100ms post stimulus onset and gradually decreasing afterwards. We next investigated the dynamics of information encoding by analyzing the optimal patterns of averaging among adjacent 10ms time bins. Notably, we observed a strong alignment between information content and dynamics, with a distinct boundary also appearing in temporal resolution between the non-informative periods 0-50ms and the informative 50-250ms intervals. Furthermore, we observed highest correlations not only at the peak of informativity, but also during periods of least information, showing their similarity in benefiting from noise reduction through averaging. Comparison with information-theoretic entropy computations confirmed our findings, further validating the observed relationship between information content and dynamic resolution.

Disclosures: **T. samiei:** None. **E. Nozari:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.04/U33

Topic: I.07. Data Analysis and Statistics

Support: RF1-DA056376
RF1-DA056376-S1

Title: Oscillatory Sparse Pattern Learning Across Time (O-SPLAT): A novel streaming model for decoding latent sources in oscillatory data

Authors: *T. ALSTON[1], P. GUPTA[2], J. M. PEARSON[3];
[1]Duke, Durham, NC; [2]Duke Univ., Durham, NC; [3]Neurobio., Duke Univ., Durham, NC

Abstract: While sophisticated neural recording technologies have made it increasingly easy to collect large, rich neural data sets comprising activity from many brain regions during natural behaviors, much of this data has yet to produce interpretable neural patterns. Typical studies look for structure by averaging neural signals over many repeats of the same behavior, but naturalistic behavior lacks this structure. Thus, what is needed are methods to effectively analyze large-scale brain responses without averaging across trials, especially in cases where the relevant patterns of brain activity change over time. Because streaming algorithms process data only once, they are ideal for both large datasets and for online/closed-loop applications (Draelos et al 2021, Gupta et

al 2024 *in prep*). Prior work from our lab has demonstrated that such algorithms can learn stable, informative data patterns and function at high input rates, but these methods do not translate readily to oscillatory signals like Local Field Potentials (LFPs), the most common data type collected by brain implants. Here, to address these challenges, we introduce O-SPLAT (oscillatory sparse pattern learning across time), a novel streaming approach that models multichannel oscillatory data driven by a collection of latent sources, each with its own power spectrum, that are sparsely active in time. Using synthetic experiments, we show that O-SPLAT can recover multichannel activity patterns under noisy conditions, can learn the latent frequency information embedded in each source, and can operate in real time at speeds of up to 25 times data acquisition. These results, along with preliminary experiments on real data, suggest that O-SPLAT is suitable for online analysis in future closed-loop experiments.

Disclosures: **T. Alston:** None. **P. Gupta:** None. **J.M. Pearson:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.05/U34

Topic: I.07. Data Analysis and Statistics

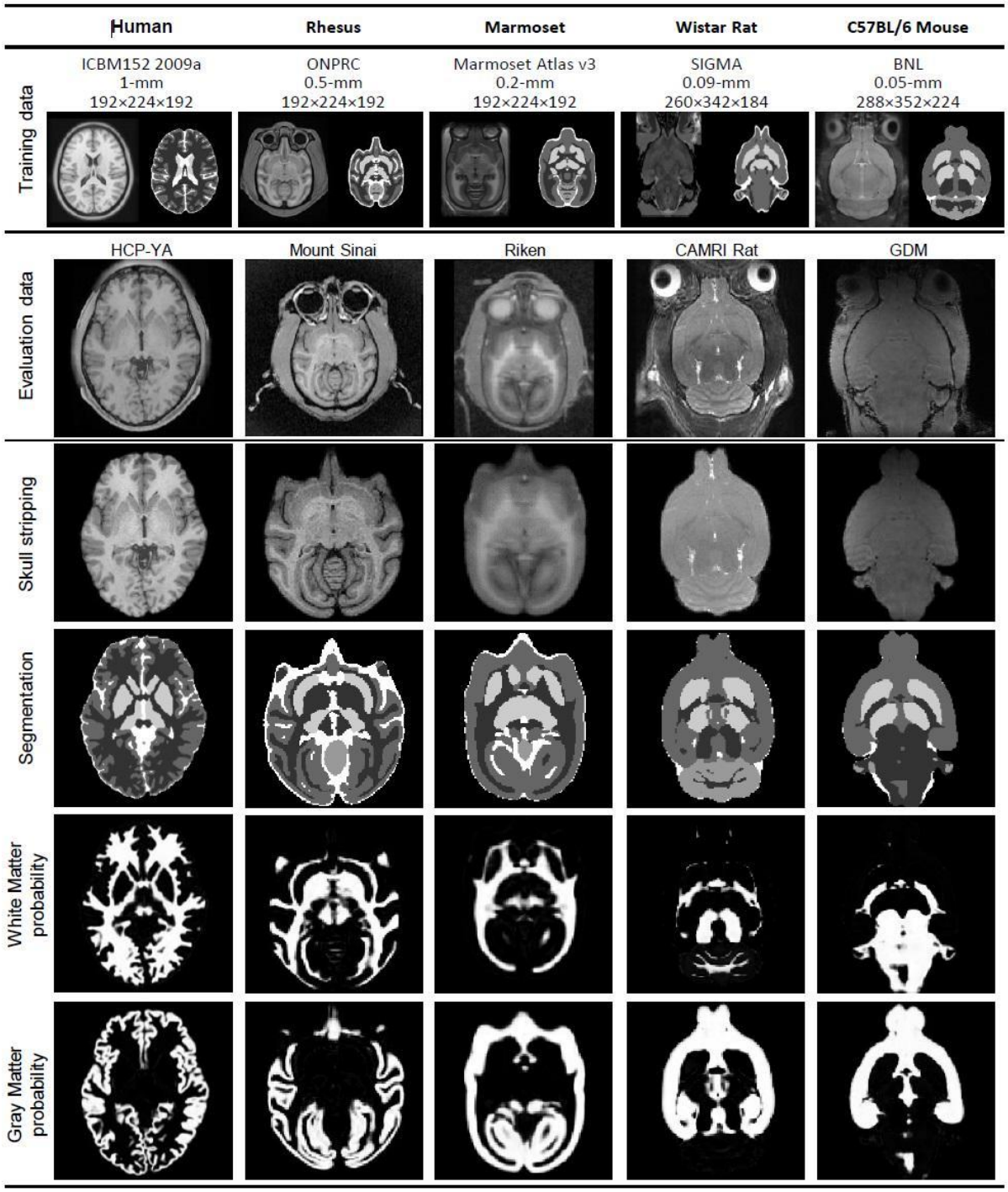
Support: R01NS120954

Title: U-net studio: a cross-species brain mri segmentation tool using template-based training and visual perception augmentation

Authors: *F.-C. YEH;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Accurate segmentation and quantification of brain regions in MRI are essential for understanding structural changes, yet the limited availability of expert-labeled data has impeded the performance of deep learning models in biomedical imaging segmentation, where labeling demands specialized expertise and manual delineation. To address this, we introduce U-Net Studio, a cross-species tool tailored for segmenting tissue and key structures in brain MRI across mice, rats, marmosets, rhesus macaques, and humans. Our model, based on the U-Net architecture (Ronneberger et al., 2015), features 3D convolutional and upsampling layers. Drawing inspiration from human visual processing, which can learn effectively from a single template, our tool employs a series of image augmentation techniques and addresses viewpoint dependence issues. This approach enables training U-Net models from scratch using publicly available brain image templates, requiring only one template at its minimum and eliminating the need for a large training sample. By integrating this augmentation strategy with a U-Net architecture and species-specific templates, our models excel in tasks such as skull-stripping, brain segmentation, and tissue probability mapping across species. Additionally, our model showcases robustness against image inhomogeneity and diverse acquisition conditions in

animals. This template-based training method effectively tackles the challenge of limited training data availability and offers significant potential for advancing deep learning applications in brain image analysis.



Disclosures: F. Yeh: None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.06/U35

Topic: I.07. Data Analysis and Statistics

Support: ZIA-MH-002920-09

Title: Funmaps: a toolbox for parcellating functional brain networks using resting-state functional mri data

Authors: *A. S. PERSICHETTI[1], J. SHAO[2], S. J. GOTTS[3], A. MARTIN[4];
[1]NIMH, Bethesda, MD; [2]Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Lab. of Brain and Cognition, NIMH/NIH, Bethesda, MD; [4]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Functional parcellations of resting-state functional magnetic resonance imaging (fMRI) data are widely used to create topographical maps of functional networks in the human brain. While such parcellation maps are highly useful for studying brain organization and function, they usually require large sample sizes to make them, thus creating practical limitations for researchers that would like to carry out parcellations on data collected in their labs. Furthermore, it can be difficult to quantitatively evaluate the results of a parcellation since networks are usually identified using a principal components analysis on the results of a single group-averaged connectivity map. To address these challenges, we developed the FunMaps toolbox: a parcellation routine that intrinsically incorporates stability and replicability of the parcellation by keeping only network distinctions that agree across halves of the data over multiple random iterations. Here, we demonstrate the efficacy and flexibility of FunMaps in three separate datasets: groups of seventy typically developing (TD) individuals and another seventy individuals with autism spectrum disorder (ASD) collected in our lab, and 450 TD individuals from the human connectome project. The FunMaps toolbox is publicly available on GitHub. It includes source code for running the parcellation and auxillary code for preparing data, quantitatively evaluating the parcellation, and displaying the results.

Disclosures: A.S. Persichetti: None. **J. Shao:** None. **S.J. Gotts:** None. **A. Martin:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.07/V1

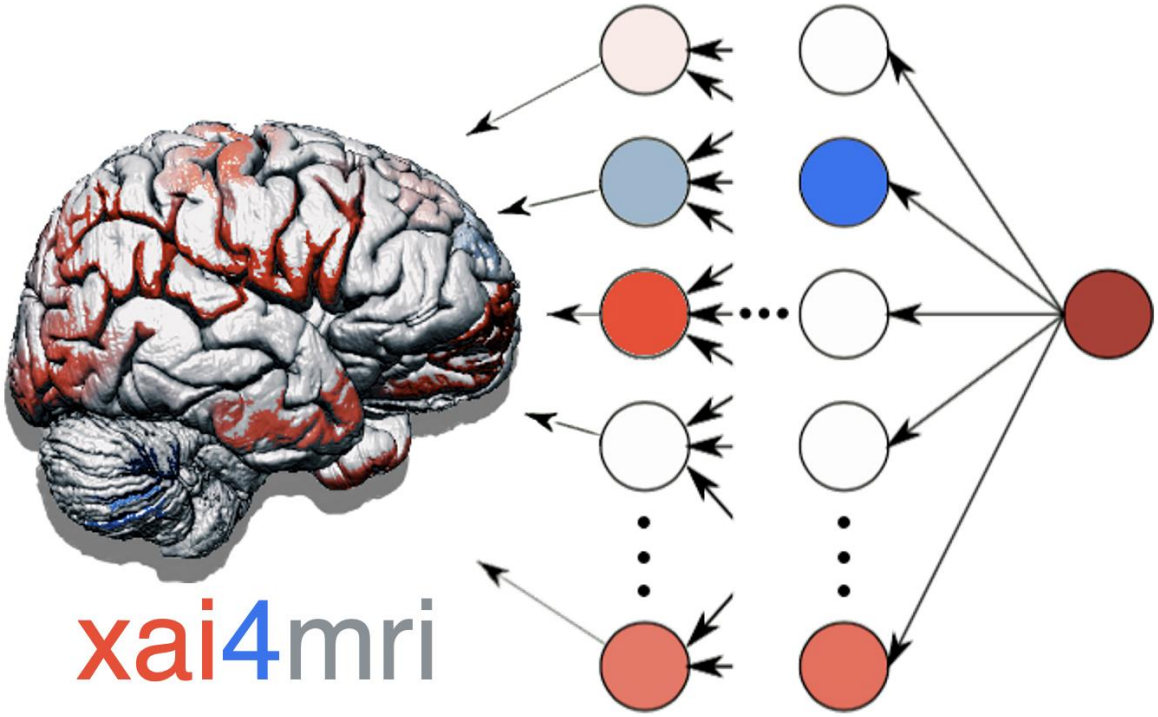
Topic: I.07. Data Analysis and Statistics

Support: BMBF Grant 01IS22065 for ACONITE

Title: xai4mri - a python toolbox for explainable deep-learning-based mri predictions

Authors: *S. HOFMANN[1], N. SCHERF[2], M. GAEBLER[3], A. VILLRINGER[1], V. WITTE[3], F. BEYER[3];
[1]Neurol., Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany; [2]Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany; [3]Neurol., Max Planck Inst. of Human Cognitive and Brain Sci., Leipzig, Germany

Abstract: Deep neural networks (DNNs) have become central tools in neuroimaging. However, even for experts, these AI models are inherently difficult to grasp, due to their large parameter space. To open the black box and determine the features that drive their decisions, new explainable AI (XAI) algorithms have been developed. Here, we introduce the Python-based *xai4mri* toolbox that combines both prediction models and XAI for neuroimaging analysis. *xai4mri* can be applied on raw and processed volumes for regression and classification tasks. Explanation maps are visually interpretable and can be used for downstream statistical analysis. *xai4mri* is for newcomers and experts in machine learning, who can apply also their own DNNs. Employing this pipeline, we showed that DNNs are highly sensitive to focal features such as white matter hyperintensities, but also to more global properties (e.g., cortical thickness). *xai4mri* can be installed using *pip*. The toolbox provides methods to effectively load whole MRI datasets:
First, users import the *BaseDateSet* from the *datasets* submodule and create a dataset class that inherits from it. The implemented class will be provided with information about the dataset it represents; it requires a method that takes a participant ID and returns the path to their MRI. Users can load pre-trained *models* (from Hofmann et al., 2022), trained on T1w, FLAIR, SWI) or initialize a new model and fit it with sampled training data. Then, with the *interpreter* submodule, model predictions can be analyzed as heatmaps with a few lines of code. The analyzer output can be visualized and further processed as statistical map.
xai4mri promises to be a tool for both data-driven exploration and hypothesis-driven research using DNN in neuroimaging, thereby complementing classical voxel-wise procedures. With its high-level API, *xai4mri* vastly simplifies the loading and processing of MRI datasets, DNN training, and the interpretation of model predictions using XAI.



xai4mri logo - tracing the voxel-level contributions to the DNN prediction.

Disclosures: **S. Hofmann:** None. **N. Scherf:** None. **M. Gaebler:** None. **A. Villringer:** None. **V. Witte:** None. **F. Beyer:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.08/V2

Topic: I.07. Data Analysis and Statistics

Support: DFG German Research Foundation 493345456
HBCD NIH Project 3U24DA055330-03S1

Title: Extended fMRIprep: a reproducible pipeline for developmental neuroimaging

Authors: *R. MCCOLLUM[1], M. GONCALVES[3], J. MOSER[1], T. MADISON[1], A. HOUGHTON[1], L. MOORE[1], M. A. STYNER[4], C. SMYSER[5], D. ALEXOPOULOS[5], J. LUNDQUIST[1], S. KOIRALA[1,6], S. M. NELSON[2,1], K. B. WELDON[1], C. MARKIEWICZ[3], R. A. POLDRACK[3], E. FECZKO[1,2], O. ESTEBAN[3,7], D. A. FAIR[1,2,6];

[1]Masonic Inst. for the Developing Brain, [2]Dept. of Pediatrics, Univ. of Minnesota, Minneapolis, MN; [3]Dept. of Psychology, Stanford Univ., Stanford, CA; [4]Departments of Psychiatry and Computer Sci., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [5]Dept. of Neurol., Washington Univ. Sch. of Med., St. Louis, MO; [6]Inst. of Child Develop., Minneapolis, MN; [7]Dept. of Radiology, Lausanne Univ. Hosp. and Univ. of Lausanne, Lausanne, Switzerland

Abstract: To preprocess functional magnetic resonance imaging (fMRI) data, researchers often create ad hoc processing pipelines that vary between studies, adding to the reproducibility crisis. fMRIprep was introduced in 2019 as a solution to the need of a robust and reproducible preprocessing workflow that can be applied to a variety of datasets. Since then, we have made several improvements that extend this pipeline's usability across the lifespan. Infant fMRIprep (AKA Nibabies) has been adapted for infant processing, which is challenging due to smaller brain size and incomplete tissue development. Both adult and infant fMRIprep can now ingest single-echo and multi-echo (ME) data. To better align with the pipeline from the Human Connectome Project (HCP), one of the first studies to use standardized brain imaging measures, fMRIprep outputs now include FreeSurfer morphometric outputs, adhere more closely to the standardized output format (BIDS), support longitudinal data, and are compatible with XCP-D, a widely used processing pipeline. ME data outputs include T2* maps, allowing for the investigation of tissue properties, like iron content, and myelination. To assess the performance of the updated pipeline, we compared connectivity matrices from fMRIprep 23.2.1 and fMRIprep-LTS to ABCD-BIDS, and found that matrices from fMRIprep 23.2.1 are significantly more similar to ABCD-BIDS matrices ($p<0.001$) than fMRIprep-LTS matrices are to either pipeline. Visual QC on the infant fMRIprep outputs demonstrated clear white and gray matter delineation and proper surface reconstruction. These results are due to several improvements. The surface workflow was updated to include MSMSulc to better capture the geometry of the gyri and sulci and direct resampling of the blood-oxygen-level dependent signal to a common reference space. We updated the volume workflow to include FSL topup distortion correction using fieldmaps and goodvoxels masking to remove high variance voxels from the surface projection, a feature also included in the HCP pipeline. Nibabies had some additional features enhancing outcomes for this age range. For example, it can intake manually edited segmentations and select different surface reconstruction methods based on the subject's age. There is also use of age specific templates to register the images to a common space. With these improvements, fMRIprep is a powerful reproducible pipeline for processing fMRI data across the lifespan.

Disclosures: R. McCollum: None. **M. Goncalves:** None. **J. Moser:** None. **T. Madison:** None. **A. Houghton:** None. **L. Moore:** None. **M.A. Styner:** None. **C. Smyser:** None. **D. Alexopoulos:** None. **J. Lundquist:** None. **S. Koirala:** None. **S.M. Nelson:** F. Consulting Fees (e.g., advisory boards); Turing Medical. **K.B. Weldon:** None. **C. Markiewicz:** None. **R.A. Poldrack:** None. **E. Feczko:** None. **O. Esteban:** None. **D.A. Fair:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Turing Medical.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.09/V3

Topic: I.07. Data Analysis and Statistics

Title: Xoani: extensible open-framework for analysis of neuroimage

Authors: *S.-H. LEE[1], Y.-Y. I. SHIH[2];
[1]Ctr. for Animal MRI (CAMRI), Neurology, and Biomed. Res. Imaging Ctr. (BRIC), The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Ctr. for Animal MRI (CAMRI), Dept. of Neurol. and Biomed. Reesearch Imaging Ctr. (BRIC), Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: The demand for standardized data to enhance reproducibility and facilitate collaboration in neuroimaging is increasingly critical. The Brain Imaging Data Structure (BIDS) is a cornerstone standard in this field, continually expanding to include various data types, such as preprocessed and analytical reports. Despite these advancements, integrating legacy software, which often adheres to unique, entrenched procedures, remains a significant challenge. Ensuring reproducibility across different stages of data processing also presents considerable challenges, as each software tool requires specific environments and dependencies. This complexity often hampers the automation of data pipelines. Modern solutions typically involve containerizing software to fit project-specific workflow frameworks; however, these efforts can suffer from inconsistencies and lack standardization, requiring considerable maintenance. XOANI (eXtensible Open-framework for Analysis of NeuroImages) is a Python-based framework designed to address these issues. It targets functional Magnetic Resonance Imaging research, adhering to BIDS standards to ensure consistent, interoperable datasets while allowing for flexible data management tailored to the needs of individual software tools. XOANI simplifies the data processing workflow, from image conversion and metadata parsing to data reconstruction, through easy-to-implement code snippets. For preprocessing, XOANI employs a containerized workload manager that orchestrates jobs on local computers connected to a network with shared storage. This setup streamlines the processing pipeline by efficiently distributing workloads across nodes using Docker Swarm, thereby reducing the complexity traditionally associated with cluster computing configurations. While currently optimized for Docker Swarm, XOANI maintains an open framework philosophy, facilitating enhancements through the XOANI Enhancement Proposal (XEP). This proposal invites collaborative efforts to extend XOANI's capabilities, enabling adaptations to various computational infrastructures like SLURM or Kubernetes and incorporating additional functionalities such as advanced analysis and visualization tools. XOANI aims to set new standards in data handling for neuroimaging, promoting effective collaboration and reproducibility across institutions without the need for extensive configuration. Initially focused on preclinical imaging, the framework has the potential to evolve into a standardized platform for executing complex analytical pipelines as BIDS expands its scope.

Disclosures: S. Lee: None. **Y.I. Shih:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

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Program #/Poster #: PSTR050.10/V4

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant R01AG079345
NIH Grant R01AG080678

Title: State-space modeling analysis provides interpretable, precise, and individualized characterizations of neural oscillations

Authors: *M. HE[1,2,3], P. DAS[4], P. L. PURDON[4,5];
[1]Stanford Univ., Palo Alto, CA; [2]Department of Psychology, Stanford University, Palo Alto, CA; [3]Department of Anesthesia, Critical Care and Pain Medicine, Stanford University, Palo Alto, CA; [4]Dept. of Anesthesia, Critical Care and Pain Med., Stanford Univ., Palo Alto, CA; [5]Bioengineering, Stanford University, Palo Alto, CA

Abstract: Neural oscillations are ubiquitous in electrophysiological recordings of human neural activity, and they have been recognized to play a fundamental role in how neurons communicate and perform computations to support adaptive cognition. Non-invasive measurement modality such as magneto-/electroencephalography (M/EEG) can readily record oscillatory signals that are primarily generated from rhythmic firing of cortical pyramidal cells. Studying such signals is of broad interests across neuroscience domains; however, existing analysis methods are largely limited to the frequency domain through Fourier analysis. This traditional approach has generated promising results to highlight the importance of neural oscillations, but it ignores distinctions between noise and signals, imposes arbitrary frequency cutoffs, and fails to capture individualized features of neural activity. Recognizing these issues as critical roadblocks to studies of neural oscillations, we have taken an alternative approach through time-domain modeling using a novel class of interpretable state-space oscillator models. Building on the idea of physical oscillating systems, we have developed a powerful suite of methods to characterize neural oscillations in electrophysiological recordings. Our existing advancements include 1) an oscillator search algorithm to answer the fundamental question about what oscillations are present beyond noise, 2) a highly interpretable decomposition of multi-channel recordings to identify coherent oscillation networks, 3) a switching state-space algorithm to detect and extract time-varying oscillations, 4) an efficient and precise estimation of phase-amplitude coupling, and 5) an empirically justified measure of aperiodic signals. To facilitate broader usage of these advanced methods, we have developed an open-source user-friendly Python library, SOMATA (State-space Oscillator Modeling And Time-series Analysis), where the methods are brought together to work synergistically. It introduces state-space model object classes, in particular oscillators, as basic building blocks and implements relevant inference algorithms as flexible computations. This library not only allows for effortless applications of the above methods, but also provides a plug-and-play platform for developing future state-space oscillator modeling methods. In this work, we showcase SOMATA using simulation studies and real neural data applications for each analysis methods and demonstrate the huge potentials of such state-space modeling approach to study neural signals.

Disclosures: **M. He:** None. **P. Das:** None. **P.L. Purdon:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.11/V5

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant 1 R01 AG056015-01

Title: Characterizing the relationship between slow wave amplitude and phase amplitude coupling during sevoflurane-induced anesthesia

Authors: ***F. TIAN**[1], M. HE[2], R. GUTIERREZ[2], O. AKEJU[1], P. L. PURDON[2];
[1]Massachusetts Gen. Hosp., Boston, MA; [2]Stanford Univ., Palo Alto, CA

Abstract: Slow wave amplitude saturation and phase amplitude coupling have been proposed as potential markers of anesthesia-induced unconsciousness, both of which appear to refer to the same underlying mechanistic principle, namely that slow oscillations measured in the EEG reflect alternating "On" and "Off" states in underlying neuronal populations that interrupt neuronal firing and thus cortical function. In this study, we seek to characterize the relationships among slow wave amplitude and phase amplitude coupling parameters, phi_mod (phase) and k_mod (amplitude), during sevoflurane-induced general anesthesia. EEG data (64 channels) were collected from 12 subjects before, during and after sevoflurane-induced general anesthesia. We first conducted baseline recordings for 10 min. Then, we increased the end-tidal sevoflurane concentration in a stepwise matter to subanesthetic (1.1%), general anesthetic (2.1%), and deep-general anesthetic (2.8%) levels, each of which was maintained for 15 min. Finally, we recorded emergence EEG data for 10 min. EEG data were analyzed using multitaper spectral and state space phase amplitude coupling methods. Phase amplitude coupling was identified predominantly in frontal and occipital regions of the brain. Strong correlation ($r = 0.6\sim0.8$, $p < 0.05$) were found between slow wave amplitude and phi_mod for frontal channels. Moderate to low level of correlation ($r = 0.2\sim0.4$, $p < 0.05$) were found between slow wave amplitude and k_mod across the brain. We also characterized end-tidal sevoflurane concentration as a function of slow wave amplitude, phi_mod, and k_mod, using mixed-effects models. Preliminary results suggest that there are significant correlations with slow wave amplitude, phi_mod and k_mod, in frontal, parietal and occipital channels. The mixed-effects modeling show significant between-subject variations for slow wave amplitude, phi_mod and k_mod, suggesting large between-subject variations in dose response. Our results suggest that both slow wave amplitude and phase-amplitude monitoring could be used to monitor anesthesia-induced unconsciousness. It is known that there is substantial between-subject variation in the magnitude of anesthesia-induced slow wave activity, suggesting that application of this marker into clinical practice could be challenging, requiring individualized assessment of the appropriate slow wave level for titration for every patient. On the other hand, the phase amplitude modulation parameters are insensitive

to subject-level differences in slow-wave amplitude, making them more readily applicable for anesthetic monitoring in a broad population of patients.

Disclosures: F. Tian: None. **M. He:** None. **R. Gutierrez:** None. **O. Akeju:** None. **P.L. Purdon:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

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Program #/Poster #: PSTR050.12/V6

Topic: I.07. Data Analysis and Statistics

Title: Specparam 2.0: spectral parameterization with time-resolved estimates and updated model forms

Authors: *T. DONOGHUE[1], B. VOYTEK[3], J. JACOBS[2];
[1]Biomed. Engin., [2]Dept. of Biomed. Engin., Columbia Univ., New York, NY; [3]Cognitive Sci., Univ. Of California, San Diego, La Jolla, CA

Abstract: In the analysis of neuro-electrophysiological recordings, recent developments have emphasized that as well as the commonly analyzed periodic or oscillatory activity, there is also prominent arrhythmic, or aperiodic activity. The distinction between periodic and aperiodic activity is important - methodologically because these two components can be conflated by common analysis approaches that do not explicitly consider the different forms of the data, and scientifically, as the two features have distinct interpretations in terms of the underlying circuit dynamics and physiological properties. In recent work, we proposed a method for parameterizing periodic and aperiodic components from neural power spectra (‘fitting-oscillations and one-over f’ or ‘fooof’), which detects and quantifying frequency-specific peaks of power (putative oscillations) over and above a separately parameterized aperiodic component that contributes power across all frequencies. Here, we present an overview of recent updates to this method, which has been generalized and renamed spectral parameterization (‘specparam’). Specparam now supports additional fitting functions that allow for different variants of periodic and aperiodic activity - as well as having improved model selection and evaluations, and in-built capabilities for time-resolved estimations. We demonstrate and evaluate these methodological updates in electrophysiological datasets, including in human intracranial recordings whereby the updated models allow for better capturing patterns of aperiodic neural activity, and in which time-resolved analyses are demonstrated to reflect transitions between brain states. Collectively, these analyses demonstrate the utility of explicitly parameterizing aperiodic and periodic neural activity, and in particular support the generalizations made to the method, by showing how the new models forms and time-resolved estimates provide novel insights into the patterns of activity and their putative interpretations that go beyond standard analyses and the initial spectral parameterization models.

Disclosures: **T. Donoghue:** None. **B. Voytek:** None. **J. Jacobs:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.13/V7

Topic: I.07. Data Analysis and Statistics

Support: NIH Training Grant 1T32NS131178-01

Title: Filtered point processes tractably capture rhythmic and broadband power spectral structure in field-based neural recordings

Authors: *P. F. BLONIASZ[1], S. OYAMA[2], E. P. STEPHEN[3];
[1]Grad. Program for Neurosci., [2]Undergraduate Program in Neurosci., [3]Mathematics and Statistics, Boston Univ., Boston, MA

Abstract: Neural field potentials (e.g., electroencephalography, EEG; local field potentials, LFP) emerge from interacting rhythmic (oscillatory) and broadband (aperiodic) biological subprocesses. Both rhythmic and broadband processes contribute to the neural power spectrum, which describes the dynamic structure in the field potentials across frequencies. While an extensive body of literature has successfully studied the role of rhythmic power underlying various diseases and brain states, only recently have researchers systematically studied characteristics of broadband effects in the power spectrum. Broadband effects can be generally categorized as 1) shifts in power across all frequencies, which correlate with changes in local firing rates (e.g., Ray and Maunsell, 2011; Scheffer-Teixeira et al., 2013) or 2) overall power spectral shape changes such as the “spectral slope” or power law exponent. Shape changes are evident in various conditions and brain states, influenced by factors such as excitation to inhibition balance (Gao et al., 2017), age (Voytek et al., 2015), and sleep states (Kozhemiako et al., 2022). In addition, broadband and rhythmic effects can interact on a sub-second timescale, e.g. broadband power is time-locked to the phase of <1 Hz rhythms in anesthesia (Stephen et al., 2020). There is a need for modeling tools that explicitly deal with both rhythmic and broadband contributors to the power spectrum and can capture their interaction to help improve the interpretability of power spectral effects. Here, we introduce a tractable stochastic forward modeling framework implemented in a python software package, FilteredPointProcesses, designed to capture both narrowband and broadband spectral effects when there's prior knowledge about the key biophysical processes involved. The framework models population-level neural recordings as the sum of filtered point processes (e.g., Bédard et al., 2006; Miller, 2010). We build on prior work by: 1) allowing time-varying firing rates by using doubly stochastic point processes with dynamic rate functions, 2) constructing a large library of biologically-inspired filters, and 3) deriving the resulting theoretical power spectra and autocovariance functions for model use cases. The framework and software package can be used

to interpret empirically observed power spectra and cross-frequency coupling effects biophysically, which bridges the gap between theoretical models and experimental results.

Disclosures: **P.F. Bloniasz:** None. **S. Oyama:** None. **E.P. Stephen:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

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Program #/Poster #: PSTR050.14/V8

Topic: I.07. Data Analysis and Statistics

Title: A novel statistical approach towards defining and estimating laterality index using task based functional magnetic resonance imaging (fmri) data

Authors: *S. CHOWDHURY[1,2,3], R. GARG[2], D. C. REUTENS[3];
[1]UQ-IITD Res. Acad., [2]Sch. of Information Technol., INDIAN INSTITUTE OF TECHNOLOGY DELHI, New Delhi, India; [3]Ctr. for Advanced Imaging, THE UNIVERSITY OF QUEENSLAND, St Lucia, Australia

Abstract: Introduction: Accurate determination of the laterality of language regions becomes critical when planning surgical resections for patients with language-related conditions to minimize the risk of postoperative language deficits. Laterality Index (LI) provides a measure of lateralization by comparing the activation levels between the left and right hemispheres within specific regions of interest (ROI) obtained from task fMRI data. However, the calculated LI values can be unreliable due to factors such as statistical threshold, signal-to-noise ratio (SNR), ROI, and task contrast to name a few. The objective of this study is to give a rigorous mathematical definition of LI under the assumptions of general linear model (GLM) and develop methods of estimation of LI under those assumptions.
Methods: We present three methods for the estimation of LI. These three successively improved estimation methods develop an interval estimate as well as a point estimate of the LI, under the assumption that the activated voxels are known using GLM analysis. Firstly, the naïve interval estimate of the LI is based on the individual interval estimates of the left and right hemispheric activations. The second method is a numerical optimization based on non-symmetric confidence levels. The third method, transformation-based approach, uses a linear rearrangement of the LI expression to obtain a tighter interval. These estimates are evaluated using bias, coefficient of variation (CV) and interval width (IW). Simulation examples are created by varying the SNR level as well as the number of task blocks in a hypothetical experiment paradigm.
Results: An increase in SNR value leads to a consistent decrease in the bias, CV and IW values for all the three methods, signifying a tighter and precise LI estimate with decreasing noise levels. The naïve method has the highest bias, CV and IW values due to its leniency, followed by a slight improvement by numerical optimisation method. However, the bias, CV and IW values is the lowest in the third method of LI estimation. Furthermore, this approach also outperforms the other two methods across all the three evaluation metrics when the number of task blocks are

increased. Interestingly, the increase in the number of task blocks is indicative of an increase in the SNR levels, thereby improving the bias, CV and IW.
Conclusion: The following study focusses on formulating a rigorous mathematical approach to formally define and explain the LI for a specified ROI in a given fMRI data. The present work can play a pivotal role in the determination of LI from language fMRI data which consists of no knowledge of any gold standard or ground truth LI value.

Disclosures: **S. Chowdhury:** None. **R. Garg:** None. **D.C. Reutens:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

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Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.15/V9

Topic: I.07. Data Analysis and Statistics

Title: The Healthy Brain Network EEG Dataset

Authors: *S. SHIRAZI[1], D. TRUONG[2], M. P. MILHAM[3], A. DELORME[4], S. MAKEIG[5]; [1]Swartz Ctr. for Computat. Neurosci., Univ. of California San Diego, San Diego, CA; [2]Electrical and Computer Engin., UCSD, La Jolla, CA; [3]Child Mind Inst., New York, NY; [4]UCSD Dept. of Neurosciences, La Jolla, CA; [5]Swartz Ctr. for Computat. Neurosci., La Jolla, CA

Abstract: The Healthy Brain Network (HBN) project, by the Child Mind Institute, is a rich collection of behavioral, neuroimaging, and biometric data from about 7,500 children and young adults aged 5-21 in the New York City area. This multimodal dataset includes MRI, fMRI, EEG, eye-tracking data, and detailed cognitive and psychiatric assessments. We have curated the electroencephalographic (EEG) recording sessions, systematically organized in the Brain Imaging Data Structure (BIDS) EEG data format, and augmented with behavioral data, personalized electrode locations, and bi-factors of psychopathology to enhance its public accessibility and readiness for analysis. HBN EEG recordings are conducted using high-density 128-channel EEG systems, capturing data during three passive tasks, including movie viewing and rest, and three interactive tasks, including sequence learning and contrast change detection. Here, following FAIR open science principles, we meticulously integrated the EEG recordings with the separately recorded behavioral response and environment data, developed detailed Hierarchical Event Descriptor (HED) annotations for each task, and submitted the augmented, fully annotated datasets to OpenNeuro.org for sharing. HBN datasets are also available on the NEMAR.org electrophysiological data portal, supporting data and metadata quality inspection, downloading, and immediate high-performance computing through the Neuroscience Gateway (nsgportal.org) for classical and machine learning analysis approaches. We performed a series of quality controls to validate the data and ensure its integrity, specifically detecting data anomalies, including data length, discontinuity, sampling rate, and completeness of crucial events. Four participant psychopathologic bi-factors (P-factor, internalizing, externalizing, and attention scores) are included in the release to provide a refined perspective on the mental health profiles

and neurodiversity of the participants. The dataset, currently including data from over 4,000 participants, will soon be enhanced with synchronous eye-tracking data and participant-specific electrical head models from participant MRI images. We intend to add more HBN participant data soon after their release by the Child Mind Institute. These multimodal data provide a comprehensive and invaluable resource for exploring developmental and cognitive neuroscience using existing and new modeling approaches.

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Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

Location: MCP Hall A

Time: Saturday, October 5, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.16/V10

Topic: I.07. Data Analysis and Statistics

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Title: Recording details of events in time-series data: The Hierarchical Event Descriptor (HED) system

Authors: *D. TRUONG[1], S. SHIRAZI[1], M. DENISSEN[2], D. HERMES[3], A. DELORME[1], K. A. ROBBINS[4], S. MAKEIG[1];
[1]UCSD, La Jolla, CA; [2]Univ. of Salzburg, Salzburg, Austria; [3]Physiol. and Biomed. Engin., Mayo Clin., Rochester, MN; [4]Computer Sci., Univ. of Texas at San Antonio, San Antonio, TX

Abstract: Capturing the details of events in experiments in a form that can be understood by both humans and machines is essential to the sharing, reusage, and large-scale analysis of neuroimaging data. The Hierarchical Event Descriptors (HED) is the only existing system that standardizes the description of experiment events. Using a common vocabulary and syntax, HED allows researchers to annotate details of any ‘things that happened’ during an experiment, including the temporal structure of the experiment itself, presentations of experiment stimuli and other sensory events, participant actions including task responses, and any data features noted during or following data collection. The HED vocabulary is extensible, in particular accommodating discipline-specific vocabularies in HED library schemas. Current schemas add clinical EEG and linguistic terms to the Standard HED schema. The HED tools ecosystem written in MATLAB, Python, and Javascript are freely available and can be integrated into other analysis software. HED is fully supported by the BIDS (Brain Imaging Data Structure) system that is becoming an integral part of the data storage standards for an ever-increasing number of neuroimaging data modalities (M/EEG, fMRI, etc.). Use of HED annotation in archived and shared datasets will make possible search across datasets for any classes of recorded events, thereby speeding analyses of single datasets and making possible efficient meta- and mega-

analyses across collections of archived and/or shared datasets using machine learning or other modeling methods.

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Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

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Title: Toward quantitative characterization of cognitive attributes using commercial brain computer interfaces

Authors: *F. ACEVES[1], W. R. GRAY RONCAL[2];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Applied Physics Lab., Johns Hopkins Univ., Laurel, MD

Abstract: Electroencephalogram (EEG) technology presents an opportunity to explore advances at the intersection of psychology, education and neuroscience. In contrast to laboratory EEGs, commercial EEGs often have more portability and convenience, but a reduction in signal quality and limited collection sites. This design optimization may make these devices beneficial for large-scale deployment in operational and educational settings. Current literature on commercial EEG for scientific applications is varied and in early stages, with promising exploratory results to discriminate between different cognitive states for attributes such as focus, pain, and stress. To explore this potential, we conducted a literature review of existing work, and acquired a popular commercial EEG system (the Muse2 headset) to develop and validate potential signal acquisition and analysis pipelines. We demonstrate a successful paradigm to easily acquire and analyze data, and explore how these methods may be used to replicate and validate existing work, especially surrounding stress and focus. Finally, we illustrate an experimental design to assess resilience and persistence, with the aim of adding quantitative measures to individuals' demonstrated grit, which has been found to correlate with long term success. This work explores how EEG analyses may more routinely provide a complementary signal to traditional survey-based performance instruments, and augment our understanding of cognition.

Disclosures: F. Aceves: None. **W.R. Gray Roncal:** None.

Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

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Topic: I.07. Data Analysis and Statistics

Title: Cloose: an open-source platform for optical brain-computer interface experiments

Authors: *V. FRANCIONI[1], A. L. BELTRAMINI[2], M. T. HARNETT[3];
[1]MIT, Cambridge, MA; [2]MIT, Somerville, MA; [3]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Brain-Computer Interfaces (BCI) have catalyzed profound advancement in both clinical and basic neuroscience research. However, technical barriers such as steep learning curves and complex synchronization requirements have impeded the widespread adoption of BCI. In response to the increasing demand for more user-friendly closed-loop experimental tools, we introduce CLOOSE (Closed-Loop Optical Open-Source Experiments), a versatile platform written in MATLAB, designed to seamlessly facilitate BCI experimentation with optical imaging approaches. CLOOSE offers a user-friendly interface to streamline experimental workflows and experimental flexibility. It interfaces with any acquisition system via a simple TCP-IP connection, allowing computational load to be distributed across two machines. We validate CLOOSE's capability to handle large-scale neural datasets with low latency, ensuring accurate real-time signal processing and precise image registration, including on sparse data, at imaging frequencies beyond 300 Hz. We further showcase CLOOSE's versatility in supporting several neurofeedback paradigms such as multiplane imaging and closed-loop optogenetic manipulations, and provide code snippets for easy experimental customization. CLOOSE also provides utility beyond neurofeedback experiments, such as online z-offset analysis, functional screening for online retinotopies and orientation selectivity, and offline ROI alignment across experimental days. CLOOSE aims to streamline, simplify, and democratize experimental design, data acquisition pipelines, and offline data processing for BCI optical experiments.

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Poster

PSTR050: Software Tools: fMRI, EEG, and LFP

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Title: A Platform for Synchronization Between CorTec BrainInterchange, Mobile Devices and a Cloud Environment

Authors: *F. MIVALT[1], F. LAMPERT[1], M. A. VAN DEN BOOM[2], W. ENGELHARDT[3], I. KIM[1], D. HERMES[4], V. KREMEN[5], N. F. INCE[6], P. BRUNNER[7], G. A. WORRELL[1], K. J. MILLER[8];
[1]Mayo Clin., Rochester, MN; [2]Dept. of Neurosurg., Mayo Clin., Rochester, MN; [3]Dept. of Neurosurg., Washington Univ. in St. Louis, St. Louis, MO; [4]Physiol. and Biomed. Engin., Mayo Clin., Rochester, MN; [5]Neurol., Mayo Clin., Rochester, MN; [6]Dept. of Biomed. Engin., Mayo Clin., Rochester, MN; [7]Dept. of Neurosurg., Washington Univ., St. Louis, MO; [8]Neurosurg., Mayo Clin., Rochester, MN

Abstract: Rationale: The next-generation implantable devices capable of continuous local field potential (LFP) sensing and adaptive neural stimulation are targeting applications of closed-loop deep brain stimulation (DBS) for epilepsy, Parkinson's disease, psychiatric disorders, and brain computer interface (BCI) for people with locked-in syndrome. Future applications of adaptive DBS and BCI will require autonomous sophisticated algorithms which inherently increase associated risks. Proactive automated monitoring of the implanted device's condition (lead integrity, battery level, and temperature) and the algorithm's performance may help mitigate these risks, even in a dynamic environment that a human brain is. Examples of potential factors affecting LFPs, and therefore autonomous algorithms, can be different behavioral states (awake-sleep), medications or aging.
Methods: We created a platform technology by integrating the CorTec BIC with the open-source BCI2000 ecosystem. Data synchronization via bidirectional communications has been achieved for mobile and implantable devices in this environment. The system was implanted in canines and LFPs were monitored for one year. The data was converted to the BIDS data structure to facilitate data sharing and collaboration.
Results: The developed system enables real-time data visualization, analysis, closed-loop adaptive therapy and demonstrates capabilities for long-term LFP monitoring. The system has proven useful for studying canine brain activity under different sensory stimulation tasks, delivering electrical stimulation, and differentiating sleep states. Precise data synchronization from mobile devices interfacing with CorTec BIC and the cloud environment was implemented as well. Preliminary data show stable electrode impedance and network communications post-implant surgery. Regular impedance checks demonstrated the practical utility of such a system for monitoring system integrity.
Conclusion: The integration of CorTec BIC with BCI2000, utilizing mobile devices and a cloud environment, enables real-time study of brain activation under different sensory tasks, detection of sleep states, and remote monitoring of the condition of the implanted device. Enhanced monitoring of implantable systems will be crucial in risk mitigation for the next generation of implantable systems with advanced closed-loop algorithms.

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