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Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Title: Effect of inorganic arsenic on monoaminergic neurons in zebrafish embryos

Authors: *J. KANUNGO[1], Q. GU[1], S. FITZPATRICK[2];
[1]NCTR/USFDA, Jefferson, AR; [2]CFSAN/USFDA, Rockville, MD

Abstract: Inorganic arsenic is a naturally occurring contaminant in foods and drinking water. We investigated the effect of inorganic arsenic on overall development and monoaminergic neurons in zebrafish. Exposure of zebrafish embryos at 5 hours post fertilization (hpf) to inorganic arsenic (sodium arsenite) induced developmental toxicity as measured by body length in 72 hpf larvae, beginning at a concentration of 300 mg/L. At 24 and 48 hpf, the embryo development appeared unperturbed upon exposure to 100 - 500 mg/L sodium arsenite. No mortality or overt morphological deformity was detected below 500 mg/L sodium arsenite. However, excessive apoptosis throughout the body of the larvae was detected starting at 200 mg/L sodium arsenite. Heart rate remained unchanged at concentrations of 100 - 400 mg/L sodium arsenite. In 72 hpf larvae, whole-mount immunohistochemistry revealed that sodium arsenite at 200 mg/L induced the development of tyrosine hydroxylase-positive (dopaminergic) neurons. However, there was no significant effect on the development of 5-hydroxytryptamine (5-HT or serotonergic) neurons at 200 or 400 mg/L sodium arsenite exposure. These results show that inorganic arsenic can alter the development of dopaminergic neurons in a vertebrate animal model, suggesting early life exposure may negatively impact human health.

Disclosures: J. Kanungo: None. **Q. Gu:** None. **S. Fitzpatrick:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: Australian Research Council Discovery Project DP210103233

Title: Identification and characterization of subnuclear domains in neuronal cells decorated by long noncoding RNAs

Authors: *S. ALTAF[1], M. J. CUMMINS[1], J. S. JUNG[2], J. MATTICK[1];
[1]Sch. of Biotech. and Biomolecular Sci., Univ. of New South Wales, Sydney, Australia;
[2]Dementia Res. Centre, Macquarie Med. Sch., Macquarie Univ., Sydney, Australia

Abstract: Long noncoding RNAs (lncRNAs) play diverse roles in chromatin dynamics and cell biology. They localize to membrane-less compartments and organelles, such as nucleoli, nuclear speckles, paraspeckles, P-granules, and G-bodies, through liquid-liquid phase separation. LncRNAs function as key regulators of neuronal processes, such as neurogenesis, synaptogenesis, neuroplasticity and remodelling, neurotransmission, and neuronal differentiation. Analysis of in situ hybridization using Allen Brain Atlas images revealed region-specific and subcellular expression patterns for over 600 out of approximately 1300 targeted lncRNAs in the mouse brain. Some of these lncRNAs exhibit specific expression in the cerebellum and hippocampus, known for regulating motor movements and cognitive processes. Notably, few lncRNAs exhibit intriguing punctate nuclear expression patterns in cerebellum and hippocampus, suggesting their association with specialized phase-separated domains. This project aims to identify and characterize the lncRNA-decorated subnuclear structures for selected lncRNAs. Verification of the Allen Brain Atlas results was performed through RNAscope and super-resolution widefield microscopy on mouse brain tissue sections. LncRNA-decorated subnuclear compartments are being purified using RNA-protein Interactome MagIC Beads and characterized through RNA sequencing and mass spectrometry. Positive control probes targeting Neat1 (paraspeckles) and negative control probes targeting bacterial RNA are used. This study will identify the role and composition of previously unknown associated subnuclear compartments, shedding light on their functions, and advancing our understanding of phase separated domains in neuronal cell biology.

Disclosures: S. Altaf: None. **M.J. Cummins:** None. **J.S. Jung:** None. **J. Mattick:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: Wellcome Trust
Waterloo Foundation
Health and Care Research Wales

Title: Mechanisms of corticogenesis in models of 16p11.2 genetic locus Copy Number Variations and their effects on the differentiation of projection neurons

Authors: O. SQUIRE[1], C. ZUGLIAN[1], I. MORELLA[1], J. HALL[1], R. BRAMBILLA[2], ***F. BEDOGNI**[1];
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Abstract: Imbalanced excitatory/inhibitory tone is a symptom shared by many neurodevelopmental disorders (NDDs). However, the mechanisms leading to tone imbalances remain elusive. Excitatory neurons of the cerebral cortex are generated during embryonic life, when proliferating cortical progenitors either regenerate themselves and re-enter the cell cycle or exit the cell cycle differentiating into postmitotic cells. It is known that the ability of progenitors to produce projection neurons populating cortical layers decreases with time. In fact, early divisions can generate neurons of both deep and upper cortical layers, whereas late divisions selectively generate upper cortical neurons. Changes in the dynamics of cortical progenitors' proliferation and postmitotic differentiation may therefore contribute to changes in the differentiation of cortical projection neurons and in how they mature and integrate in neuronal networks. This is a critical step, as changes in such dynamics may produce an anatomical substrate that increases the risk of imbalanced excitatory/inhibitory tones. In this study we focus on Copy Number Variations (CNVs) of the 16p11.2 locus. These are within the most frequent genetic rick factor of neurodevelopmental impairments, with symptoms including autism spectrum disorders, intellectual disabilities, epilepsy and, in the case of locus duplication, schizophrenia. Our interest in the animal models of 16p11.2 CNVs is therefore based on its clinical relevance, but also on the fact that it offers the possibility of testing how two opposite conditions (either locus deletion or duplication) may converge onto similar outcomes at the level of network functions. Our data suggest that locus deletion drives excessive proliferation of progenitors, with increased number of both radial glial cells and intermediate progenitors. In contrast, locus duplication reduces the number of such progenitors. Intriguingly, postmitotic projection neurons in both deletion and duplication display similar impairments, namely differences in the representation of deeper and upper cortical layer neurons. More significantly, by using markers of neuronal networks activity (immediate early genes), we unmasked similarly patterns of altered network activity through different region of the cerebral cortex, including the prefrontal cortex. Cumulatively, our data suggest that similar differentiation impairments may arise from seemingly opposite regulation of proliferation driven by either deletion or duplication of the 16p11.2 locus. This evidence might therefore support the existence of common pathogenic mechanisms at the root of multiple NDDs.

Disclosures: O. Squire: None. **C. Zuglian:** None. **I. Morella:** None. **J. Hall:** None. **R. Brambilla:** None. **F. Bedogni:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Support: BICAN U01

Title: Molecular logic of cell type development and diversification in mouse visual cortex

Authors: *Y. GAO[1], C. VAN VELTHOVEN[1], C. LEE[2], E. THOMAS[1], B. TASIC[3], Z. YAO[4], H. ZENG[4];
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Abstract: The mammalian brain is highly heterogeneous and develops through a series of temporally regulated events that are crucial for its proper function. The mechanisms underlying the development of different cell types are not fully understood. Single-cell RNA-sequencing offers a unique opportunity to systematically study cell types across the entire temporal range of brain development. In this study, we present a dataset of single-cell transcriptomes obtained from densely sampled prenatal (E11.5 to E18.5) and postnatal (P0 to P56) stages of development of the mouse visual cortex (VIS). The dataset includes 66,134 prenatal and 502,922 postnatal cells collected from VIS and processed by single-cell RNA-sequencing using the 10x Genomics v3 platform. We developed a computational approach to construct the cell type trajectories based on the transcriptomic profiles, revealing critical differentiation events and birth dates of different cell types. Furthermore, we explored the temporal dynamics of transcriptomes at the subclass and supertype levels and identified genes associated with lineage bifurcations or neuronal maturation events. In addition to neurogenesis in prenatal stages, there are additional cell types emerging during the eye opening period. Collectively, our analysis provides the most detailed transcriptomic examination of cell type development in the cortex and reveals the molecular logic underlying the continuous series of refinements of cell-type identities during development.

Disclosures: Y. Gao: None. **C. van Velthoven:** None. **C. Lee:** None. **E. Thomas:** None. **B. Tasic:** None. **Z. Yao:** None. **H. Zeng:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R21 1R21NS105436-01
Michigan Translational Research and Commercialization (MTRAC) Grant; Michigan Economic Development Fund
Tech Transfer Network postdoctoral fellowship support (Michigan Economic Development Fund)

Campbell Foundation Research Grant Program
GVSU Student Summer Scholars Program

Title: Modified nato3 gene can upregulate engrailed1 expression in human embryonic stem cells

Authors: O. SWEENEY[1], S. MATHEW[2], G. OKROS[3], *M. DELANO-TAYLOR[2];
[1]Grand Valley State Univ., Allendale, MI; [2]Biomed. Sci., Grand Valley State Univ., Allendale, MI; [3]Cell. and Mol. Biol., Grand Valley State Univ., Allendale, MI

Abstract: Nato-3, a basic helix-loop helix (bHLH) transcription factor, is expressed in the floor plate region of the central nervous system (CNS), giving rise to dopaminergic (DA) neurons which are important in the pathogenesis of Parkinson's Disease (PD). Other labs have shown that a mouse knockout of Nato-3 in vivo leads to an attenuation of DA neurons by half. We have previously published that overexpression of Nato3 leads to an increase in genes related to DA neurogenesis in restricted regions of the embryonic brain. Phosphorylation of Nato3 may be one mechanism that regulates the expression of genes important in DA neurogenesis. In the developing chick embryo we found that expression of a phosphorylation mimicking mutant of Nato3 (PM-Nato3) at putative phosphoacceptor residues Threonine 101 and Serine 140 increased Engrailed-1 (En1) protein expression broadly in the anterior and posterior midbrain (n=3) relative to empty vector (n=5) or wild type Nato3 (n=3; $p < 0.05$). We show that co-expression of Nato3 with constitutively active protein kinase A (C-alpha subunit) consistently elevated En1 expression relative to Nato3 expression alone (n=5) in a mouse midbrain cell line (SN4741 cell line). Further, the effect of C-alpha subunit on Nato3 elevation of En1 expression was reduced with the mutation of Nato3 at serine 140 (S140A) in the same cell line (n=3). We hypothesized that we may see similar results in human embryonic stem cells (hESC) and found expression of the human form of PM-Nato-3 (T99E/S138D) had significant and sustained expression of EN1 mRNA expression with hESC cultured in standard 3N media (DMEM/F12, N2 (GIBCO), 5 μg/ml insulin, 1mM L-glutamine, 100 μM non-essential amino acids, 100 μM 2-mercaptoethanol, 50 U/ml penicillin, 50 mg/ml streptomycin, 1 μM dorsomorphin (Tocris) or 500 ng/ml mouse Noggin-CF chimera (R&D Systems) and 10 μM SB431542 (Tocris)) after three days of culture ($p < 0.05$) and continuing at 25 days of culture ($p < 0.05$ n=2). These data support the hypothesis that the putative phosphorylation site of Nato3 may be a key regulator of a gene important in DA neurogenesis and survival. Understanding the regulation of key dopaminergic genes in human embryonic stem cells may yield insights into development of cell based therapies.

Disclosures: O. Sweeney: None. **S. Mathew:** None. **G. Okros:** None. **M. Delano-Taylor:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Title: Effects of Exercise-Induced Plasma-Derived Extracellular Vesicles on Adult Neurogenesis, Astrogliogenesis, and Microvascular Density in the Hippocampus

Authors: P. RAVI[1], M. G. CONNOLLY[2], D. I. ROSU[3], A. FLIFLET[1], M. D. BOPPART[1], J. S. RHODES[4];
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Abstract: Exercise enhances cognitive performance and volume of the hippocampus in humans and rodent models. In rodents, voluntary wheel running increases adult hippocampal neurogenesis between 2 to 5-fold depending on the genotype, and level of running. This increase in neurogenesis is accompanied by increased microvasculature and astrogliogenesis specifically in the hippocampus. Given that hippocampal atrophy is associated with many common neurological disorders such as anxiety, depression, PTSD, Alzheimer's disease, epilepsy, and normal aging, understanding how to increase hippocampal neurogenesis has obvious advantages. However, despite decades of research, the mechanisms by which exercise increases hippocampal neurogenesis remain largely unknown. One possible important contributor could be extracellular vesicles (EVs). EVs are increasingly recognized to play a significant role in intercellular communication. During exercise, active muscles release EVs that contain a multitude of signaling molecules (ExerVs). However, whether ExerVs are sufficient to increase hippocampal neurogenesis, astrogliogenesis and microvasculature remains unknown. The present study examined the effects of injecting plasma derived ExerVs isolated from exercising male C57BL/6J mice on these hippocampal traits in male sedentary C57BL/6J. EVs were isolated from both sedentary mice (SedV) and mice with access to a running wheel (ExerV) and then injected into a new group of sedentary mice twice a week for 4 weeks. An additional cohort of sedentary mice were injected with PBS to serve as the control. BrdU (bromodeoxyuridine) injections were given the first 10 days to label dividing cells. Preliminary results show sedentary mice receiving ExerV injections had 1.2-fold increased numbers of BrdU-positive cells compared to sedentary mice receiving SedV injections or PBS injections. Approximately 88% of the BrdU+ cells were co-labeled with the mature neuronal marker, NeuN, and 5% were co-labeled with the mature astrocyte marker, S100, similarly in all the groups. Taken together this result suggests ExerVs increased both the number of new astrocytes and new neurons in the hippocampus. Microvascular measurements are currently underway using collagen IV immunohistochemistry and stereology. This experiment only had 5 animals per group and is currently being repeated to determine whether results are replicable. If ExerVs can increase hippocampal neurogenesis, astrogliogenesis, or microvasculature, and their effects are translatable in humans, they may provide a useful novel therapeutic for reversing hippocampal atrophy associated with the aforementioned conditions.

Disclosures: P. Ravi: None. **M.G. Connolly:** None. **D.I. Rosu:** None. **A. Fliflet:** None. **M.D. Boppart:** None. **J.S. Rhodes:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: New Jersey Health Foundation Grants (Z.L.M., V.M.)
Connecticut Science Fund Grant (V.M.)

Title: Stable tunneling nanotube-like connections develop between postmitotic daughter cells that do not complete cytokinesis in a neuronal cell culture model of Alzheimer's and Parkinson's disease

Authors: P. VAID, Z. MURESAN, *V. MURESAN;
Pharmacology, Physiol. and Neurosci., New Jersey Med. Sch., Rutgers Univ., Newark, NJ

Abstract: Neurodegenerative diseases typically lead to the abnormal aggregation of neuronal proteins that interfere with neuronal function and ultimately cause neuronal death. Alzheimer's Disease (AD), a severe form of dementia that causes brain damage and cognition loss at old age, is characterized by initial accumulation of toxic protein species - amyloid-β peptide (Aβ) and hyperphosphorylated Tau protein (pTau) - in a small population of neurons in the entorhinal cortex and/or the locus coeruleus. Most cases of Parkinson's disease (PD) are characterized by the presence of α-synuclein aggregates, which accumulate within the neuronal soma (Lewy bodies) and the neurites (Lewy neurites). As the diseases progress, the toxic protein species gradually spread throughout the vulnerable brain regions, likely through a process that involves neuron-to-neuron transmission. It was proposed that the transfer of the toxic species from the neuron where they have been generated to the recipient neuron could occur through thin, channel-like connections, known as tunneling nanotubes (TNTs). Whether TNTs form early during brain development (and are preserved through adult life) or during adult life or at old age is not known. Neuronal cell lines, originating in brain neurons, are ideal systems to address this question. Using metabolically stressed, locus coeruleus-derived neuronal cells (CAD), we identified a novel mechanism of generation of cell-to-cell connections that structurally resemble TNTs. We found that such connections form between daughter cells that fail to complete cytokinesis after mitosis and remain permanently connected. Such TNTs, identified via the acetylated microtubules that persist in the region of the midbody, form while CAD cells proliferate, and are maintained throughout, and after, differentiation. We found that the TNT-like connections increase in length as the cells they connect migrate in different directions, and withstand extreme mechanical stress. These TNTs have various length and caliber, differ in shape (straight or curved), rigidity (stretched or relaxed), and may develop branches. The cells linked via such TNTs acquire a neuronal phenotype that is undistinguishable from that of cells without TNTs, extending multiple, long neurites. We showed that these TNT-like connections contain a large variety of proteins and protein aggregates typically present in AD and PD (e.g., pTau, TDP-43, α-synuclein). Based on these results with neuronal cultures, we propose that, in

the in vivo brain, TNTs that enable interneuronal transfer of pathogenic species in AD and PD are established during embryonic development and persist in the adult and old brain.

Disclosures: P. Vaid: None. **Z. Muresan:** None. **V. Muresan:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.08/Web Only

Topic: A.01. Neurogenesis and Gliogenesis

Support: FLUG STDF grant # 46721
JESOR ASRT grant #5275

Title: Adipose Mesenchymal Stem Cells Differentiation towards Cells Expressing Neuronal Markers via Orchestrate CREB-1, NCAM, & Ephrin Signaling Pathways

Authors: *S. H. A. I. SHOUMAN, Jr[1], A. SAMY[2], A. ABOUSHANAB[3], A.-E. ABOZIAD[2], E. BADR[2], N. EL-BADRI[3];
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Abstract: Reprogramming of adipose-derived mesenchymal stem cells (ADMSCs) into neurons is a promising autologous source for neural regeneration. However, the underlying mechanisms driving this differentiation process are elusive. We developed a predictive computational workflow for stem cell differentiation using transcriptomic profiles of primary cell samples from the FANTOM5 project. Applying our approach to ADMSCs, we identified several significantly enriched pathways involved in neuronal differentiation. Based on our analysis, we proposed three candidate pathways including neural cell adhesion molecule (NCAM), Eph-Ephrin signaling pathways, and cAMP-response element-binding protein 1 (CREB1) phosphorylation. These proposed pathways introduce a stepwise differentiation of ADMSCs into cortical neurons following an intermediate differentiation step into neural stem cells (NSCs). Eph-Ephrin and NCAM are primary modulators in early neuronal morphogenesis. CREB1 phosphorylation enhances neuronal maturation and function. We validated these computational data by applying a two-step differentiation protocol. For the first step of induction into NSCs, a combination of valproic acid, SB431542, and LDN193289 was utilized; for the second step of human-induced neurons (hiNs), B27, N2, and N-acetyl cysteine were employed. After 5 days of treatment, induced-NSCs (iNSCs) showed significant upregulation of NSCs markers, including Nestin, NKX-1, ASCL, FOXG, SOX-2, and Olig-2 expression. Compared to ADMSCs, iNSCs showed upregulated expression of NCAM and EFNB2. Additionally, iNSCs were able to form neurospheres. In the second step, the neuronal markers TUB III, MAP-2, and NeuroD were

upregulated over the following five days. When comparing the hiNs group to the control, GRINs and GAD transcripts—markers for glutamatergic and GABAergic neurons, respectively—were substantially expressed. Phosphorylated CREB1 protein was significantly overexpressed during the last five days. CREB1 induces differentiation into neuron-like cells through RAS-P-ERK1/2 pathways activation confirmed by qPCR and Western blot. This data proposed novel combinatory candidate pathways which orchestrate a step-wise neuronal differentiation of ADMSCs, advancing personalized cell-based therapy in neurodegenerative diseases.

Disclosures: S.H.A.I. Shouman: None. **A. Samy:** None. **A. AbouShanab:** None. **A. Aboziad:** None. **E. Badr:** None. **N. El-Badri:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.09/A8

Topic: A.01. Neurogenesis and Gliogenesis

Support: Phase II SBIR grant from NIH/NIMH R44MH119621

Title: The anti-retroviral Biktarvy reduces in vitro iPSC-derived NPCs viability and disrupts differentiation and neuronal calcium activity.

Authors: *C. G. RINES[1], K. L. GORDON[2], N. A. SUAREZ[2], A. S. SMITH[3], K. L. JORDAN-SCIUTTO[4], J. H. PRICE[1], P. M. MCDONOUGH[5];
[1]Vala Sci., Inc., San Diego, CA; [2]Biol., Vala Sci. Inc., San Diego, CA; [3]Vala Sci., San Diego, CA; [4]Dept Oral Med., Univ. of Pennsylvania, Lansdale, PA; [5]Vala Sci. Inc, San Diego, CA

Abstract: Pregnant people living with HIV receive combination antiretroviral therapy (cART) for their own health and to prevent perinatal HIV transmission. While prenatal cART has increased health and neurodevelopmental outcomes for children exposed to HIV, clinical studies and preclinical toxicology research suggest that cART may affect the central nervous system during fetal development, even in children who remain HIV negative. cART may also impair adult hippocampal neurogenesis (which shares mechanisms with fetal neurogenesis) and contribute to HIV-Associated Neurocognitive Disorders (HAND). It is therefore crucial to develop predictive assays for assessing neurotoxic effects of cART on neurons and neural progenitor cells (NPCs). We developed a 384-well screening platform to quantify neurotoxic effects of anti-retrovirals (ARVs) on the developing CNS. The platform used human induced pluripotent stem cell (hiPSC)-derived NPCs to examine effects on cell viability, DNA replication, SOX2 expression and differentiation. In this study we measured possible toxicity of Biktarvy, a combination drug consisting of bictegravir, tenofovir alafenamide and emtricitabine, given to HIV-positive women during pregnancy. We found that a 3-day Biktarvy treatment impairs viability, DNA replication and nuclear SOX2 expression in two separate NPC lines (one

differentiated in-house and one purchased from Elixirgen Scientific). To assess Bictarvy's effects on cell fate and differentiation of NPC, we evaluated changes in intracellular calcium flux and in neuron to glia cell ratios We cultured Elixirgen NPCs in neural differentiation media in the presence of various doses of Biktarvy (at concentration up to and including maximum plasma concentration (Cmax)) for 6 weeks. All tested Biktarvy doses disrupted NPC differentiation into neurons, measured by a decrease in MAP2 positive cells and VGLUT2 expression in the cultures.
For high doses of Biktarvy (including Cmax of each of its constituent ARVs), 3 weeks of exposure caused significant morphological changes to the MAP2-positive cells. For low doses of Biktarvy (including one tenth the Cmax of its constituent ARVs), 6 weeks of exposure also altered intracellular calcium transient activity in the differentiated neurons. Together, these results suggest that cART can affect neural progenitor survival in vitro and may also affect pathways associated with neurogenesis. Our screening platforms can be used to identify safer cART regimens and to screen for therapeutics that can mitigate cART-induced developmental neurotoxicity.

Disclosures: C.G. Rines: None. **K.L. Gordon:** None. **N.A. Suarez:** None. **A.S. Smith:** None. **K.L. Jordan-Sciutto:** None. **J.H. Price:** None. **P.M. McDonough:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.10/A9

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 1R15HD114135-01

Title: An Analysis of the Tweety Gene Family Member's 1 and 3 and their Role During Neural Development in Xenopus laevis

Authors: *M. ROYSTER[1], A. WEST[2], G. HUSSEY[2], S. PILLAI[2], M. S. SAHA[3];
[1]Col. of William and Mary, Midlothian, VA; [3]Biol., [2]Col. of William and Mary, Williamsburg, VA

Abstract: This project explores the roles of the tweety 1 (*ttyh1*) and tweety 3 (*ttyh3*) genes in the development of the *Xenopus laevis* nervous system. Highly expressed in the nervous system, dysfunctional expression of these genes is associated with many pathologies. Analysis of these genes in our lab suggest that *ttyh1* plays a role in regulating neural progenitor cells. To decipher this complex regulation, overexpression and knockout embryos of *ttyh1* and *ttyh3* were created. To accomplish overexpression, vectors were designed and synthesized containing *ttyh1* and *ttyh3* gene cDNA to produce capped mRNA. To accomplish knockout, target sequences were identified in the tweety gene coding regions, and CRISPR Cas9 sgRNAs were designed to guide

the Cas9 protein to knockout both genes. These constructs were utilized to induce perturbation of Tweety signaling via injection into *X. laevis* embryos at the two cell stage. Additionally, Green Fluorescent Protein (GFP) mRNA was utilized as an injection control and tracer. Mutation efficiency was assessed using TIDE (Tracking of Indels by Decomposition) analysis at a variety of developmental stages, and further downstream transcriptomic analysis was conducted via *in situ* hybridization (ISH) and RNA sequencing.
ISH results for embryos fixed after injection with *ttyh3* mRNA to induce overexpression showed no significant change in the expression of Neural Beta Tubulin (NBT), a marker for postmitotic neurons, or SRY-box 2 (Sox2), a marker for neural progenitor cells following perturbation. These results suggest complex pathways regulating the differentiation of neural stem cells. Bioinformatic analysis comparing the upstream regions of *ttyh1* and *ttyh3* to identify conserved regulatory elements was also conducted using the mVISTA database. Conservation analysis at the vertebrate level yielded no universal conservation within the intergenic regions of *ttyh1* or *ttyh3*. However, significant conservation was found between the short and long homologs of both genes in *X. laevis*, suggesting complex modes of gene expression regulation.

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Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.11/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01HD092593
F31HD098886

Title: Lack of placental Allopregnanolone delays cortical development

Authors: *H. A. LACAILLE[1], J. O'REILLY[2], D. BAKALAR[3], J. SALZBANK[4], C.-M. VACHER[1], A. A. PENN[1];
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Abstract: Neuroplacentology is an emerging field of research that focuses on the impact of placental factors on fetal brain development. Approximately 380,000 infants per year in the United States abruptly lose placental support upon premature birth, and more than 10% of pregnancies may be affected by more insidious placental dysfunctions such as preeclampsia or infection. Abnormal fetal brain development or injury can lead to life-long neurological impairments, including autism, epilepsy, and cognitive impairments. Our work focuses on the

hypothesis that placental endocrine dysfunction or specific placental hormone loss may place many thousands of fetuses at risk of life-long neurodevelopmental impairments each year. One such hormone is allopregnanolone (ALLO, 3α, 5α-tetrahydro progesterone), a conserved hormone produced by the placenta in humans and rodents during mid-to-late gestation (the period most affected by preterm birth). We have developed a conditional mouse model of placental ALLO loss that results in cerebellar white matter abnormalities correlated with autistic-like behavior in male offspring (Vacher et al. 2021). We are now focusing on the impact of placental ALLO loss on the developing cerebral cortex via RNA-seq analysis across developmental ages, i.e. Embryonic day 17.5 (E17.5), Postnatal day 0 (P0), P7, P15, and P30. Utilizing gene ontology and biological theme comparison methods, we highlight the alteration of common pathways across developmental stages linked to synaptic activity, i.e. channel activity, transporter activity, and neurotransmitter activity. To further understand the maturation of synapses in our model of placental ALLO loss, we calculated a maturation index based on the average of up versus down-regulated genes included in the GO term GABAergic synapse (GO:0098982, 134 genes) or Glutamatergic synapse (GO:0098978, 658 genes). The results demonstrate dysmaturation in both synapse subtypes. To complement our mouse model, we have directly assessed ALLO exposure and withdrawal using human cortical organoids. ALLO treatment and withdrawal alters neuronal maturation, as measured by shifts in neuronal specification genes (MASH1, FOXG1, NSE, and SST) in human cortical organoids. Specifically, ALLO enhances the maturation rate of ventral forebrain organoids, a phenomenon that is transiently reversed after its withdrawal. Overall, we demonstrate that placental ALLO loss delays cortical maturation, helping us define the role of the placenta in shaping long-term neurological disorders and potentially pointing to new therapies based on replacing endogenous placental hormones.

Disclosures: H.A. Lacaille: A. Employment/Salary (full or part-time):; Columbia University. **J. O'Reilly:** None. **D. Bakalar:** None. **J. Salzbank:** A. Employment/Salary (full or part-time):; Columbia University. **C. Vacher:** A. Employment/Salary (full or part-time):; Columbia University. **A.A. Penn:** A. Employment/Salary (full or part-time):; Columbia University.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.12/A11

Topic: A.01. Neurogenesis and Gliogenesis

Support: Supported by NIH R01NS124660

Title: Modeling a human GSX2 disease variant which alters DNA binding capacity and leads to a hypomorphic phenotype in mouse

Authors: *L. TWEEDIE[1,2], S. QIN[3], R. R. WACLAW[4], K. J. CAMPBELL[5];
[1]Developmental Biol., Dept. of Pediatrics, Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [2]Medical Scientist Training Program, University of Cincinnati College of Medicine, Cincinnati, OH; [3]Developmental Biol., Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [4]Exptl. Hematology and Cancer Biol., Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [5]Developmental Biol., Cincinnati Children's Hospl, Cincinnati, OH

Abstract: The neuronal and glial subtypes generated during CNS development arise from progenitors that are patterned by the restricted expression of transcription factors (TFs) along the dorsal-ventral (D-V) and anterior-posterior axes of the developing brain and neural tube. The homeobox TF Gsx2 is required for correct D-V patterning in the lateral ganglionic eminence (LGE) of the ventral telencephalon by specifying distinct neuronal subtypes such as striatal projection neurons while inhibiting gliogenesis. Germline *Gsx2* null mice are not viable postnatally and show severe dysgenesis of the striatum (the main component of the basal ganglia). A recent report in humans (De Mori et al. 2019, *Brain*, **142**:2965), identified a homozygous null GSX2 allele and another homozygous mutation within the homeodomain, changing the "Q" to "R" at amino acid 251 (i.e. $GSX2^{Q251R}$). Both mutations were viable, resulting in severe dysgenesis of the basal ganglia and neurological symptoms including dystonia and spastic tetraparesis. While the loss of *Gsx2* in mouse has previously been studied, it is unclear how this $GSX2^{Q251R}$ variant impacts striatal development. Therefore, we generated a mouse model with the analogous mutation ($Gsx2^{Q252R}$) using a CRISPR-Cas9 approach. Importantly, the $Gsx2^{Q252R}$ protein is observed to be stable and nuclear localized in mutant embryos. $Gsx2^{Q252R/Q252R}$ mice exhibit a truncated LGE, leading to striatal dysgenesis, similar to but less severe than that seen in a *Gsx2* null. These mice also show an upregulation of the compensatory gene *Gsx1* and subtle alterations of corticofugal trajectories, both of which are more pronounced in *Gsx2* null mice. Isothermal titration calorimetry (ITC) in combination with electrophoretic mobility shift assays (EMSAs) using $Gsx2^{Q252R}$ protein indicate an approximately 4-fold reduction in binding affinity at TATTA high affinity sites, as well as a switch in low affinity site preference, from Q50 sites that WT Gsx2 prefers, to K50 sites generally bound by TFs such as Otx2 and Six3. We therefore hypothesized that this point mutation in the homeodomain leads to an altered Gsx2 gene regulatory network (GRN) that is only partially conserved. We performed bulk RNA-seq analysis on dissected LGEs to compare genes differentially regulated as compared to WT mice. Interestingly, a subset of genes are uniquely up- or down-regulated in $Gsx2^{Q252R}$ mice and not in *Gsx2* null mice, supporting our hypothesis of an altered GRN. To compare *in vivo* $Gsx2^{Q252R}$ and WT Gsx2 DNA binding, we have generated ${}^{2xFLAG}Gsx2^{Q252R}$ mice for use in CUT&RUN assays. The new data set will be compared with our previously published CUT&RUN data set obtained from ${}^{2xFLAG}Gsx2$ mice.

Disclosures: L. Tweedie: None. **S. Qin:** None. **R.R. Waclaw:** None. **K.J. Campbell:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.13/A12

Topic: A.01. Neurogenesis and Gliogenesis

Support: Arsenov Foundation
Knowledge Foundation
The Zvi and Ofra Meitar Family Fund
NIH

Title: The hierarchy of neurogenesis in hypophysis, epiphysis and retina in early human embryos.

Authors: *I. BYSTRON;
Univ. of Oxford, Oxford, United Kingdom

Abstract: It is universally accepted that all neurons of the retina are produced from progenitor cells in the retinal neuroepithelium, and that the pituitary placode contributing to the formation of hypophysis is not neurogenic. Here we provide the evidence that the human eye, at the earliest stages of its development, contains a unique neuronal population migrating from the brain, and that the oral ectoderm of the invaginating Rathke's pouch generates migratory neurons. Moreover, the first neurons in the dorsal diencephalon including presumptive pineal eye emerge from the edge of the fusing neural folds. We used a set of neuronal and proliferative markers to reveal the phenotypic characteristics and migratory potential of early stem cell niches. We were able to reconstruct cells by high-resolution volume rendering of multichannel 3D data sets from a Zeiss confocal microscope. Early embryonic tissue was obtained from the Human Developmental Biology Resource UK. The mode of neural tube closure in humans is different from that in other animal species. The first neurons expressing neuron-specific beta 3 tubulin appear at the level of fusion of the neural folds in the dorsal diencephalon at E31. They extend leading processes towards the fusion line, and sparse neurons with similar bipolar morphology are seen in adjacent cephalic ectoderm comprising neural crest cells. The neuronal development in the human retina starts with early neurons invading the retina from the diencephalon. We call these unusual hypothalamic cells Meitar neurons. These cells might be important in the cascade of developmental events leading to the formation of the human retina and the optic nerve. Surprisingly calbindin (CB) immunoreactivity was confined to the cycling progenitors of the dorsal diencephalon including epiphysis, but also in the peripheral retina. We suggest that the newborn neurons in these areas, utilizing CB as a regulator of intracellular calcium, contribute to the formation of the dorsal thalamus and the retina. We also found bipolar neurons scattered through the mesenchyme extending processes into the retina. These migratory cells were distinct from the population of the neural crest cells delaminating from the closing neural tube. Invasion of the developing retina by extraretinal neurons has not been described in any other mammalian species. The genetic and molecular mechanisms that underlie the relationship between precocious neurons of the pituitary placode, Meitar neurons and periocular neurons remain to be elucidated.

Disclosures: I. Bystron: None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.14/A13

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Neurosurgeon Research Career Development Program
NIH DP1 Director's Pioneer Award
DUMC Holland Trice Scholars Program
Klingenstein-Simons Fund
Whitehall Foundation

Title: Exploring the functional circuit properties of human caudal ganglionic eminence interneurons

Authors: E. A. MATTHEWS[1], J. B. RUSS[2], S. ZHAO[3], Z. HUANG[4], ***D. G. SOUTHWELL**[1]; [1]Dept. of Neurosurg., Duke Univ., Durham, NC; [2]Pediatrics, Duke Univ., Durham, NC; [3]Dept. of Neurobio., Duke Univ., Durham, NC; [4]Dept. of Neurobio., Duke Univ. Med. Ctr., Durham, NC

Abstract: Comparative anatomical and transcriptomic studies indicate that the primate neocortex contains a greater proportion of GABAergic interneurons derived from the caudal ganglionic eminence (CGE) (Džaja et al., 2014; Krienen et al., 2020). CGE-derived interneurons are concentrated in upper cortical layers and are distinguished by largely non-overlapping expression of the marker genes *VIP* and *LAMP5*. In rodents, CGE interneurons, particularly Vip+ types, form relatively abundant projections onto other interneurons, thereby exerting disinhibitory functions in cortical microcircuits. While it has been hypothesized that the expansion and specialization of primate CGE interneurons could give rise to human cognitive abilities, a lack of experimental strategies has impeded understanding of CGE interneuron function in the human cortex (Lee et al., 2023). Here we applied CellREADR, a novel RNA sensing tool for cell-type specific access (Qian et al., 2022), to investigate the function-defining intrinsic physiological properties and synaptic outputs of CGE-derived interneurons in human temporal cortex. By engineering CellREADR sensors to human *CALB2* (Calretinin) RNA sequences, we gained strongly biased access to CGE interneurons in organotypic slices prepared from neurosurgical tissue specimens. Targeted patch clamp recordings of 164 cells from 15 subjects yielded a rich picture of the diverse intrinsic physiological properties of CGE interneurons. A notable feature of many human CALB2+ interneurons was their sharp responsiveness to current injections (steep input-output curves) and their high maximal action potential firing rates. Consistent with their high gain functions, in baseline conditions, 75% of cells fired action potentials from the resting membrane potential, with some cells sustaining firing rates >10Hz. PatchSeq transcriptional characterization allowed us to align recorded cells to published cellular atlases and provided further evidence for the targeting of CGE interneuron classes (primarily *VIP* class interneurons). Last, by expressing optogenetic effectors in CALB2+ interneurons, we found that the targeted cell cohort formed functional GABAergic projections onto both excitatory and inhibitory interneuron types. Together these experiments advance a novel and impactful approach for cell

type-specific access in live human neural circuits. By leveraging CellREADR's capacity for specific, scalable, and programmable cellular access, this study has advanced tools for human cellular neuroscience while furthermore elucidating some of the cellular design of human cortical inhibitory circuits.

Disclosures: E.A. Matthews: None. **J.B. Russ:** None. **S. Zhao:** None. **Z. Huang:** None. **D.G. Southwell:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.15/A14

Topic: A.01. Neurogenesis and Gliogenesis

Support: FAPESP # 2015/24001-1 and 2020/11352-9,

Title: Platelet Activating Factor Receptor (PAFR) regulates neural fate determination

Authors: *C. B. DEL DEBBIO, *B. DALMASO;
Univ. of Sao Paulo, Sao Paulo, Brazil

Abstract: The Ciliary Epithelium (CE) of adult mammalian eyes contains a quiescent population of retinal progenitor/stem cells that are able to proliferate, generate neurospheres in vitro and differentiate into functional retinal neurons. Despite this regenerative potential, the neuronal differentiation efficiency is low, probably due to the presence of regulatory mechanisms and inhibitory factors. Platelet-Activating Factor (PAF) is a lipid mediator present during retinal development. PAF together with its receptor (PAFR) demonstrated inhibitory effects on retinal progenitor cell cycle and neuronal differentiation in mammalian developing retinas. To investigate the role of PAF and PAFR in CE cells during neurospheres formation, we separated CE cells from Balb/c wild type mice from retina, sclera and iris. The Pigmented Epithelium (PE) cells were cultured with growth factors (FGF and EGF, 10 and 20 ng/ml) to form neurospheres, and treated with PAFR agonist (cPAF, 100 nM) or antagonist (PCA4248, 10 μM). After 7 days in culture, we analyzed neurospheres size and number and expression of stem cells markers by PCR and Immunohistochemistry. We observed that retinal progenitor cells within the neurospheres expressed PAFR protein and transcripts levels similarly to the original pigmented epithelial cells from CE. Neurospheres treated with PAFR agonist (cPAF) increased the expression of markers related to differentiated epithelial cells (*palmd*), and decreased stem cell markers (*pax6*, *nanog*, *sox2*, and *nestin*). On the other hand, neurospheres treated with PAFR antagonist (PCA4248) increased in number and stem cell markers. In conclusion, our results suggest that inhibition of PAF signaling through its receptor increased tem cells markers expression and the number of neurospheres, probably trough the regulation of the cell cycle. However, activation of PAF signaling was able to decrease the stem cell profiles expression and

increased differentiated cells transcripts. The information gleaned from this study may provide valuable insight into the cellular and molecular events that underlie the reprogramming response of CE cells and the mechanism of retinal differentiation.

Disclosures: C.B. Del Debbio: None. **B. Dalmaso:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.16/Web Only

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01NS117918
NIH Grant R21NS104394
NIH Grant R21NS119732
Ann L. Jones Spinal Cord Regeneration Research Fund

Title: Crispr/cas9-mediated miR-375 knockdown during astrocyte-to-neuron reprogramming

Authors: *X. CHEN[1], H. LI[2];
[1]Dept. of Neurosci. & Regenerative Med., Augusta Univ., Augusta, GA; [2]Dept. of Neurosci. & Regenerative Med., Med. Col. of Georgia at Augusta Univ., Augusta, GA

Abstract: Astrocyte-to-neuron (AtN) reprogramming holds great promise in regenerative medicine, yet its mechanisms remain elusive. Our recent findings highlighted the significant induction of miR-375 during neurogenic factor-induced neuron reprogramming, showcasing its pivotal role in averting apoptosis when overexpressed. Here, we investigate the necessity of miR-375 for the survival and maturation of induced neuronal-like cells through loss-of-function experiments. Initial attempts to suppress miR-375 expression using miR-375 decoy during neurogenic factor-induced AtN reprogramming proved inadequate. Consequently, we turned to CRISPR/Cas9, a potent genome editing tool capable of disrupting miRNA biogenesis directly by inducing mutations in pre-miRNA sequences. We designed CRISPR/Cas9 constructs with single guide RNAs targeting specific biogenesis processing sites of miR-375 and delivered them via lentivirus to three cell lines: human embryonic kidney (HEK) 293T, human glioblastoma U251, and primary human cortical astrocytes (HA). Single cell colonies of U251 cells were collected after infection and drug selection. By employing T7EN1 assay, we detected cleavage at target loci of miR-375 and confirmed the presence of insertion/deletion (indel) mutations adjacent to the protospacer adjacent motif (PAM) through DNA sequencing. Surprisingly, miR-375 loss was only evident in 293T cells (which exhibit high miR-375 expression) and not in U251 and HA cells (with weak miR-375 expression) as determined by qRT-PCR. However, upon induction with neurogenic factors including Neuronal Differentiation 1 (NeuroD1), Neurogenin 2 (Neurog2), and Achaete-scute homolog 1 (ASCL1), lentiCRISPR-gRNAs-miR-375 significantly

reduced miR-375 expression in U251 and HA cells. No loss of miR-375 was observed in the control group. These results indicate that CRISPR/Cas9-mediated miR-375 knockdown may be contingent upon cellular baseline levels of miR-375, and CRISPR/Cas9 system can robustly inhibit induced miR-375 expression. The functional impact of miR-375 knockdown is being tested during AtN reprogramming.

Disclosures: X. Chen: None. **H. Li:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.17/A15

Topic: A.01. Neurogenesis and Gliogenesis

Support: FONDECYT iniciacion 11230857

Title: Exploring the effects of D-serine and inflammation on oligodendrocyte precursor cell fate in mouse primary cell cultures

Authors: *S. BELTRAN-CASTILLO[1,2], J. ESPINOZA[1], I. E. CISTERNA[1], V. A. SILVA[3]; [1]Ctr. Integrativo de Biología y Química Aplicada, Univ. Bernardo O'Higgins, Santiago, Chile; [2]Facultad de Ciencias de la Salud, Escuela de Terapia Ocupacional, Universidad Bernardo O'Higgins, Santiago, Chile; [3]Ctr. Integrativo de Biología y Química Aplicada, Univ. Bernardo O'Higgins, Santiago, Chile

Abstract: D-serine (DS), a dextro amino acid, modulates glutamatergic NMDAR-mediated transmission. Previous studies have shown that inflammation and TGFβ can regulate the expression of serine racemase, the enzyme responsible for synthesizing DS, in primary microglial cell cultures. Additionally, an increase in DS release during brain inflammation has been reported. Given that oligodendrocytes (OLs) and oligodendrocyte precursor cells (OPCs) express NMDAR, we aimed to investigate the effects of DS and inflammation regulators like lipopolysaccharide (LPS) and TGFβ on OPC fate in mouse primary OPC cell cultures.We enriched a PDGFRα(+) OPC cell population using Magnetic Activated Cell Sorting (MACS) technology from neonatal mouse brain (P0-P3) and evaluated the effects on OPC fate at DIV6 following treatment with DS (1-10μM), with or without LPS (1μg/mL) or TGFβ1 (2ng/mL) administered at DIV5. Identity markers of OPC states, such as PDGFRα, Olig2, and MBP, along with markers for neurons (NeuN), astrocytes (GFAP), and microglia (Iba1), were used to characterize our cultures. Apoptosis was evaluated using TUNEL stain.Our isolation method yielded an average of 3.0 × 10^5 OPCs per brain, predominantly PDGFα(+), NeuN(-), with less than 0.1% IBA1(+) cells and 0.2% GFAP(+) cells. Similar to findings in other studies, we observed an increase in cells expressing Olig2, O4, or MBP, along with a population of GFAP(+) cells at DIV6, suggesting that mouse OPCs exhibit bipotentiality, capable of

differentiating into either more complex and arborized OLs or GFAP(+) astrocytes. Under control conditions, OPCs PDGFα(+) exhibited a 39.2% ± 6.0% apoptosis rate. However, while LPS did not increase apoptosis, treatment with DS (10μM) or TGFβ1 reduced the rate of OPC apoptosis in the absence (18.8% ± 6.0% and 14.7% ± 4.0%, respectively) or presence of LPS (12.6%±3.8% and 8.2%±4.9%, mean ± SEM). Similar results were detected in MBP(+) cells (Control 38.7%±10%, DS 18.1%±4.6%, and TGFβ1 20.6±5.7%). Preliminary data suggest that DS promotes apoptosis in Olig2(+) cells, while promoting the emergence of MBP(+) cells.Our findings suggest that OPC maturation or death may partly depend on inflammatory cues and DS. Further investigation into the involvement of microglia and astrocytes in DS-mediated OPC fate is warranted. Furthermore, we are currently investigating the transition of OPCs to GFAP-positive cells in ongoing experiments, as this process may have implications for mature OL outcomes. The elucidation of those mechanism could impact the design of treatments for demyelinating diseases.

Disclosures: S. Beltran-Castillo: None. **J. Espinoza:** None. **I.E. Cisterna:** None. **V.A. Silva:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.18/A16

Topic: A.01. Neurogenesis and Gliogenesis

Title: Involvement of a ubiquitin ligase RMND5A in the proliferation to differentiation transition of human neural stem/precursor cells

Authors: *T. NAKAGAWA[1], K. HATA[2], Y. IZUMI[2], H. NAKASHIMA[1], T. MATSUDA[1], S. KATADA[1], T. BAMBA[2], K. NAKASHIMA[1];
[1]Dept. of Stem Cell Biol. and Med., [2]Med. Inst. of Bioregulation, Kyushu Univ., Fukuoka, Japan

Abstract: Human cerebral cortex has a tremendous number of neurons and is quite large compared to that of other mammals, suggesting that human cerebral cortex has a specific developmental mechanism. Human neural stem/precursor cells (NS/PCs), which are the origin of all neural cells in the cortex, can proliferate for a much longer period than those of other mammals during brain development. Therefore, human NS/PCs can generate numerous neurons, enlarging the cortex. However, it is unclear how human NS/PCs increase their proliferative capacities. In this study, we explored the molecular mechanisms underlying specific properties of human NS/PCs. We performed gene knockout (KO) screening using a human gene-targeted guide RNA (gRNA) library and a human iPS cell-derived NS/PC cell line (AF22) to search for key genes: KO of the genes accelerates transition from proliferation to differentiation of AF22, promoting neuronal differentiation. In this screening, lentiviral vectors were first used to theoretically introduce a single gRNA and Cas9 into AF22 to create a single-gene KO AF22

population. We then differentiated the transduced AF22 mutants for 10 days and a gRNA sequence library for next-generation sequencing (NGS) was prepared from immature neurons collected by flow cytometry-activated cell sorting with anti-CD133 and anti-CD24 antibodies. We also made a gRNA sequence library for NGS of undifferentiated AF22. After NGS analysis, we identified several genes of which gRNAs were enriched in the immature neuronal population. By checking whether the deletion of the identified genes decreases proliferation and promotes neuronal differentiation of AF22, we found that the deletion of *RMND5A*, which encodes an E3-ubiquitin ligase and component of the CTLH complex, dramatically decreased proliferation and promoted neuronal differentiation of AF22. To verify the mechanisms of how RMND5A inhibits neuronal differentiation in AF22, we performed proteome analysis of RMND5A-depleted AF22. The proteome analysis revealed that cell cycle-related proteins were downregulated whereas cell cycle exit and neuronal differentiation-related proteins were upregulated. In addition, the STING database-based network analysis showed that upregulated proteins in RMND5A-depleted AF22 were involved in some biological processes, such as mitochondrial metabolism, mTOR, and Wnt signaling pathways. Taken together, it is suggested that RMND5A maintains a proliferative state while suppressing NS/PC differentiation by regulating various signaling pathways during human cortical development.

Disclosures: T. Nakagawa: None. **K. Hata:** None. **Y. Izumi:** None. **H. Nakashima:** None. **T. Matsuda:** None. **S. Katada:** None. **T. Bamba:** None. **K. Nakashima:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.19/A17

Topic: A.01. Neurogenesis and Gliogenesis

Support: Korea NRF Grant RS-2024-00351160
Korea NRF Grant 2020R1C1C101024514
Korea NRF Grant 2022M3E5E801739512

Title: Anoctamin 1 regulates GABA-dependent Ca^{2+} influx in ventral Radial glia of the medial ganglionic eminence

Authors: *G.-S. HONG[1], K. KIM[2], B. KANG[2];
[1]Korea Inst. of Sci. and Technol. (KIST), Seoul, Korea, Republic of; [2]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: Radial glia (RG), an early neural stem cell (NSC), located in ventricular zone (VZ) of subpallium undergo symmetric and asymmetric division under the influence of intrinsic and extrinsic factors. In a previous study, we observed high expression of *Ano1* transcripts in *Fabp7+Sox2+* vRGs of the medial ganglionic eminence (MGE) from E11.5 to E14.5. Through

patch clamp experiments conducted on embryonic brain slices (E12.5 and E14.5), vRGs in the MGE exhibited robust ANO1 currents under voltage clamp. The current-voltage (IV) curve confirmed the outwards rectifying pattern characteristic of ANO1 channels. To ratify the mechanisms associated with ANO1 in RG, we explored the potential neurotropic factors implicated in ANO1 activation in cultured NSCs. Results showed activation of ANO1 induce Ca^{2+} influx in cultured NSCs. Additionally, application of GABA on cultured NSCs triggered Ca^{2+} influx, and this GABA-induced $[Ca^{2+}]_i$ increase was blocked by treatment with Ani9, indicating that GABA-induced Ca^{2+} influx is facilitated by the cooperative action of ANO1 and the $GABA_A$ receptor. Furthermore, patch experiments revealed Cav channels were not detected in vRG on E12.5 and E14.5 slices. Our finding demonstrates the functional expression of Ano1 in RGs during brain development and suggest a cooperative role of ANO1 and the $GABA_A$ receptor in calcium influx in RGs. Given the critical role of calcium in RG division, we propose that ANO1 may play a role in regulating vRG cell fate.

Disclosures: G. Hong: None. **K. Kim:** None. **B. Kang:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.20/A18

Topic: A.01. Neurogenesis and Gliogenesis

Title: Left/right neuronal asymmetry is regulated by the Hox gene mab-5 in caenorhabditis elegans

Authors: T. BARNEY, A. ROLFSON, S. BENNETT, *S. R. TAYLOR;
Dept. of Cell Biol. and Physiol., Brigham Young Univ., Provo, UT

Abstract: Neurons share a common core genetic program, but also display striking diversity in morphology and function. Here we describe previously undocumented transcriptional asymmetries between the left and right neurons in the Sublateral Dorsal Q-derived (SDQ) pair in *Caenorhabditis elegans.* Single-cell RNA sequencing of adult animals revealed hundreds of differentially expressed genes between SDQR and SDQL, including several genes encoding neuropeptides and neuropeptide receptors. Using confocal imaging of endogenously tagged reporter alleles, we have validated differential expression of two neuropeptides: *nlp-64* in SDQR and the insulin-like neuropeptide *ins-17* in SDQL. We show that these patterns of differential expression are established in the first larval stage, shortly after the birth of the SDQ neurons, and persist into adulthood. Asymmetric expression of *nlp-64* is regulated by the asymmetric expression of the Hox transcription factor *mab-5*, as *nlp-64* is expressed in both SDQR and SDQL in *mab-5* loss of function mutant animals. These data indicate that in addition to establishing anterior to posterior identity during early development, Hox genes may also be involved in patterning left/right asymmetries in neuronal tissues.

Disclosures: T. Barney: None. **A. Rolfson:** None. **S. Bennett:** None. **S.R. Taylor:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.21/A19

Topic: A.01. Neurogenesis and Gliogenesis

Support: CDMRP Grant NF200109
CFC International

Title: Cellular signaling impacts on GABAergic cortical interneuron development; drugs, genes and the usual suspects

Authors: A. M. STAFFORD[1], D. PACHECO CRUZ[2], B. M. DEVRIES[3], J. CARR[1], L. SCHIPPER[1], H. M. HOFFMANN[4], *D. VOGT[1];
[1]Michigan State Univ., Grand Rapids, MI; [2]Michigan State Univ. Neurosci. Program, Grand Rapids, MI; [3]Michigan State Univ., East Lansing, MI; [4]Animal Sci., Michigan State Univ., East Lansing, MI

Abstract: Cortical GABAergic interneurons are a highly diverse group of cells that acquire their properties through genetic programming, local environmental cues, and more recently appreciated cellular signaling processes that may either connect the two latter processes and/or be independent of each. These unique interneurons facilitate local microcircuit inhibition onto other neurons to create a local network that the brain utilizes to interpret sensory inputs into actions. These processes and the balance between both somatostatin and parvalbumin expressing interneurons is extremely important. Herein, we explore the role of the MAPK pathway in these events and ways in which this pathway may be managed pharmacologically. We found that hyperactivating the MAPK pathway, which represents many RASopathy patients, led increased SST interneurons at the expense of PV expressing interneurons as well as behavioral changes. These alterations were recapitulated in other RASopahty models, suggesting this is a shared feature and may apply to many MAPK models. Specifically, we found that disturbing the MAPK pathway had a direct impact upon GABAergic cortical interneuron cardinal transcription factors, including LHX6, ARX and SATB1. Herein, we further explore these findings and how they may respond to FDA-approved drugs that may be repurposed to help those with a RASopathy.

Disclosures: A.M. Stafford: None. **D. Pacheco Cruz:** None. **B.M. Devries:** None. **J. Carr:** None. **L. Schipper:** None. **H.M. Hoffmann:** None. **D. Vogt:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.22/A20

Topic: A.01. Neurogenesis and Gliogenesis

Support: CIHR project grant
BCCHR catalyst grant

Title: Single-cell RNA analysis reveals different underlying molecular networks regulated by Pax6 in specific cerebellar glutamatergic neurons

Authors: J. T. YEUNG[1], R. SCHWARTZ[2], M. KE[1], P. PAVLIDIS[2], D. GOLDOWITZ[3]; [1]Med. Genet., Univ. of British Columbia, Vancouver, BC, Canada; [2]Psychiatry, Univ. of British Columbia, Vancouver, BC, Canada; [3]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The paired box transcription factor Pax6 plays an important and multivalent role in cerebellum (CB) development. Our previous work has shown that all three glutamatergic cerebellar cell types express Pax6 during development and are variously affected by the loss of *Pax6* in a cell type specific manner. In the *Pax6*-null Small Eye (*Sey*) mutant, the Tbr1+cerebellar nuclear (CN) neurons are absent due to apoptosis; the granule cells (GCs) are disorganized due to perturbed migration and delayed differentiation; and the unipolar brush cells are significantly reduced due to a combined perturb in neurogenesis and apoptosis. The pleiotropic phenotypes of the *Sey* mutant CB highlight the importance of identifying the Pax6 regulatory gene network(s) in each cell type. To this end, the transcriptomes of each cell type were assessed utilizing single-cell RNA sequencing (scRNA-seq) technology. Cerebellar single-cell samples were collected at three timepoint (embryonic day 13, 15 and 18) from *Sey* and control littermates. These timepoints correspond to the key developmental time frames of Pax6 action on the cell types in question. A transcriptomic analysis and comparison between control and *Sey* were performed to determine cell-type specific gene profiles and identify differentially expressed (DE) genes in the *Sey* CB. Our pilot scRNA-seq analysis using cells from the whole CB found that the GC transcriptomes are dramatically altered, where GCs from different genotypes form distinct clusters. On the other hand, as expected from previous findings in the *Sey* CB where GABA-ergic lineages are unaffected, transcriptomes of these cells are very similar between genotypes. To focus on the lineages affected by the loss of Pax6, we enriched for the glutamatergic cell types by FACS sorting cells that expressed GFP under the control of Atoh1. Atoh1 is expressed in all glutamatergic cells in the CB and is crucial for development. The transcriptomic analysis of these enriched glutamatergic cells shows that the clusters that correspond to Tbr1+ CN neurons are only represented by widltype cells. On the other hand, *Sey* mutant cells are overrepresented in the clusters that correspond to the Olig2+ CN neurons. This finding suggests that the loss of Tbr1+ CN in the *Sey* mutant may be due to a change of cell fate in addition to the previously described increased cell death. The analysis also identified an extensive list of DE genes in the *Sey* transcriptomes. The direct molecular targets of Pax6 will be determined using CUT&Tag technology that detects DNA sequences bound by Pax6. The information emerging from these studies will shed light on the etiology of disease states that are associated with Pax6 mutations.

Disclosures: J.T. Yeung: None. **R. Schwartz:** None. **M. Ke:** None. **P. Pavlidis:** None. **D. Goldowitz:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.23/A21

Topic: A.01. Neurogenesis and Gliogenesis

Support: Indiana University Start-up funding

Title: Chromatin regulation of cortical enhancers and their role in neuronal fate decisions

Authors: S. WARREN[1], B. EL FARRAN[1], A. CHOUDHURI[2], *M. BAIZABAL[3]; [1]Biol., Indiana Univ., Bloomington, IN; [2]Biol., Indiana Univ., BLOOMINGTON, IN; [3]Biol., Indiana Univ. Bloomington, Bloomington, IN

Abstract: Cortical neurogenesis and neuronal differentiation are determined by cell type-specific regulation of transcriptional enhancers via chromatin modifications. However, it is not well understood how the coordinated activity of chromatin-modifying enzymes in neural stem cells (NSCs) programs later stages of neuronal differentiation. We previously reported that the non-canonical histone H3 lysine 9 (H3K9) methyltransferase PRDM16 is specifically expressed in NSCs of the mammalian forebrain[1, 2]. PRDM16 activity in NSCs is necessary to program the migration of upper-layer neurons and their final position, thereby controlling the layered organization of the cerebral cortex[1]. PRDM16 regulates transcriptional enhancers in the mouse cortex and we recently showed that this activity is evolutionarily conserved and is also critical for human brain development[3]. Here, we used a series of biochemical and genomics approaches to identify multiple PRDM16-interacting partners in cortical NSCs. We will present evidence and discuss a model in which PRDM16 recruits a complex of chromatin-modifying enzymes at enhancers, resulting in histone H3 deacetylation, histone H3 lysine 4 demethylation, and the control of later stages of neuronal differentiation. Our findings provide insights into the epigenetic regulation of developmental cell decisions. This knowledge will be fundamental, in our view, to design novel therapies based on reprogramming cell identity and function in neurological disorders.1. Baizabal, J.M., et al. Neuron 98, 945–962 (2018).2. Garcia, M. T., Baizabal, J. M., et al. Development 147 (2020).3. Suresh, V., … Baizabal, J.M.*, Reiner, O*. Oxford Open Neuroscience 3, 1–16 (2024).

Disclosures: S. Warren: None. **B. El Farran:** None. **A. Choudhuri:** None. **M. Baizabal:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.24/A22

Topic: A.01. Neurogenesis and Gliogenesis

Support: BSCRC Training Grant
BSCRC Innovation Award
NIH Grant MH124018

Title: Defining cell-specific gene regulatory programs in the developing human neocortex

Authors: *C. K. VUONG[1], S. NICHTERWITZ[3], B. SHAFIE[2], L. DE LA TORRE-UBIETA[2]; [1]Psychiatry, [2]UCLA, Los Angeles, CA; [3]Karolinska Institutet, Stockholm, Sweden

Abstract: The human neocortex is responsible for our most distinguishing cognitive and social capabilities, often impaired in neuropsychiatric disorders. Previously, we found that genetic variation causing risk for neuropsychiatric disorders and influencing cognition, also regulates gene expression programs of the developing human neocortex during neurogenesis. However, the gene regulatory mechanisms governing cortical neurogenesis remain to be characterized. Here we leverage human neural stem cell models, organotypic slice cultures, and transcriptome and epigenome profiling to identify and functionally characterize gene regulatory elements (GREs) regulating human corticogenesis. We outline a strategy to generate a cell-type specific functional map of GREs, using a pooled CRISPR interference (CRISPRi) screen in differentiating human neural progenitor cells and organotypic slices to modulate the activity of hundreds of GREs. In pilot studies, we demonstrate efficient knockdown of transcription factors active during neurogenesis using our pooled CRISPRi strategy, and find significant changes in cell type composition and gene expression patterns upon loss of regulatory proteins enriched in progenitors and developing neurons. Applied to GREs regulating corticogenesis, these studies will provide insight into human-specific gene regulatory mechanisms of corticogenesis, and help translate genetic findings into human disease mechanisms.

Disclosures: C.K. Vuong: None. **S. Nichterwitz:** None. **B. Shafie:** None. **L. De La Torre-Ubieta:** None.

Poster

PSTR317: Molecular Mechanisms and Environmental Influences on Neuronal Development and Differentiation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR317.25/A23

Topic: A.01. Neurogenesis and Gliogenesis

Support: U01MH108898
R01MH124890
R21MH134401
K99HD111686
2021 NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

Title: Cell-type-resolved mosaicism reveals clonal dynamics of the human forebrain

Authors: *C. CHUNG[1], X. YANG[1], R. F. HEVNER[2], J. SCHLACHETZKI[3], J. G. GLEESON[1]; [1]Neurosciences, [2]Pathology, [3]Cell. and Mol. Med., UCSD, La Jolla, CA

Abstract: Debate remains around anatomic origins of specific brain cell subtypes and lineage relationships within the human forebrain. Thus, direct observation in the mature human brain is critical for a complete understanding of its structural organization and cellular origins. Here, we utilize brain mosaic variation within specific cell types as distinct indicators for clonal dynamics, denoted as cell-type-specific Mosaic Variant Barcode Analysis. From four hemispheres and two different human neurotypical donors, we identified 287 and 780 mosaic variants (MVs), respectively, that were used to deconvolve clonal dynamics. Clonal spread and allelic fractions within the brain reveal that local hippocampal excitatory neurons are more lineage-restricted than resident neocortical excitatory neurons or resident basal ganglia GABAergic inhibitory neurons. Furthermore, simultaneous genome-transcriptome analysis at both a cell-type-specific and single-cell level suggests a dorsal neocortical origin for a subgroup of DLX1+ inhibitory neurons that disperse radially from an origin shared with excitatory neurons. Finally, the distribution of MVs across 17 locations within one parietal lobe reveals that restriction of clonal spread in the anterior-posterior axis precedes restriction in the dorsal-ventral axis for both excitatory and inhibitory neurons. Thus, cell-type resolved somatic mosaicism can uncover lineage relationships governing the development of the human forebrain.

Disclosures: C. Chung: None. **X. Yang:** None. **R.F. Hevner:** None. **J. Schlachetzki:** None. **J.G. Gleeson:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.01/A24

Topic: A.05. Axon and Dendrite Development

Support: Craig Neilsen Foundation Pilot Grant 727694
NIH Grant R01NS131662
NYS Grant DOH SCRIB IDEA C37712GG

Title: Klhl14-cre as a novel tool for investigation and manipulation of axon targeting and innervation by bulbar-cervical corticospinal neurons

Authors: *A. LAMMERS[1], J. LUSTIG[1], P. PATEL[1], J. KAISER[1], J. M. CONNER[2], P. L. NGUYEN[3], E. AZIM[2], V. V. SAHNI[1,4,5];
[1]Burke Neurolog. Inst., White Plains, NY; [2]MNL-E, Salk Inst., San Diego, CA; [3]Neurosciences, Univ. California San Diego, San Diego, CA; [4]Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY; [5]Weill Cornell Graduate School of Medical Sciences, New York, NY

Abstract: The corticospinal tract (CST) facilitates skilled, precise movements, which necessitates that corticospinal neurons (CSN) establish segmentally specific connectivity with spinal circuitry. Recent work has identified CSN-intrinsic molecular determinants that regulate CSN axonal projections to specific segmental levels of the neuraxis and that these are expressed by CSN subpopulations that project to distinct levels of the neuraxis. In the present study, we establish the use of a newly generated Klhl14-T2A-Cre knock-in reporter mouse line to investigate axonal projections of a specific CSN subpopulation, CSNBC-lat. Breeding these mice with reporter mice shows recombination across multiple cell types and did not recapitulate the known specificity of Klhl14 expression by CSNBC-lat. However, by using conditional anterograde and retrograde labeling during development, we identify this specificity of Cre expression. We establish AAV-mediated gene delivery in Klhl14-T2A-Cre mice as an approach to reliably analyze CSNBC-lat axon targeting. We also confirm that this approach can be utilized to perform gain-of-function experiments which in turn identifies known regulators of CSN axon targeting - Crim1 and Cbln1. Finally, using intersectional viral labeling, we establish that Klhl14+ CSNBC-lat show topographical specificity of axonal projections within the brainstem. Our results establish this strategy as a novel approach for in vivo testing of candidate gene function in controlling context-appropriate CSN axon guidance in a relatively high-throughput manner.

Disclosures: A. Lammers: None. **J. Lustig:** None. **P. Patel:** None. **J. Kaiser:** None. **J.M. Conner:** None. **P.L. Nguyen:** None. **E. Azim:** None. **V.V. Sahni:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.02/A25

Topic: A.05. Axon and Dendrite Development

Support: Mohn Research Center of the Brain; 2021TMT04
Norges Forskningsråd Centre of Excellence grant (Centre for Algorithms in the Cortex, 332640

Title: Proteomic characterization of Dentate Gyrus specific growth cones in the first postnatal week

Authors: *M. KRAUSE[1], K. KRONBERG[2], G. QUATTROCOLO[2];
[1]Kavli Instiute for Systems Neurosci., NTNU, Trondheim, Norway; [2]Kavli Inst. for Systems Neurosci., NTNU, Trondheim, Norway

Abstract: Growth cones (GC) are the extreme end of the growing axon, highly motile structures that explore the environment and guide the growth of the axons in specific directions towards their postsynaptic target. Their pathfinding is influence by interaction with local cues. How these interactions and the invasion of different target regions affect the proteomic contents of GC is still unclear. We decided to use the simple organization of the hippocampal circuit to address this issue, specifically focusing on the Dentate Gyrus (DG). The DG is a subregion of the hippocampus (HP) receiving its major input from the entorhinal cortex (EC). The major output region of the DG is the CA3 subregion of the HP. GC of innervating EC fibers reach the CA3 and the DG border around postnatal day (P) 3, fully invading the DG by approximately P5. To understand how growing axons towards and in the DG change during the early postnatal days we analyzed the proteomic composition of hippocampal- (HP-GC) and DG-specific growth cones (DG-GC). We extracted GC on P1, P3, and P5 from wildtype mice. Using shotgun sequencing, we analyzed GC samples, identifying over 5500 proteins in total. By comparing DG-GC to total HP-GC preparations, we were able to identify proteins specifically enriched or depleted in the DG at the different timepoints. P1 samples exhibit the highest number of significantly enriched and depleted proteins, which decreases with age. Interestingly, each timepoint displayed a distinct set of enriched/depleted proteins with only a minimal overlap between P1 and P3. Gene ontology term analysis for biological processes revealed that DG-GC specific proteins, especially at early timepoints, are associated with different aspects of translation (mitochondrial, at pre- and post-synapse), regulation of mRNA metabolism, cellular component disassembly, as well as synapse pruning. Conversely, DG-GC depleted proteins are linked to regulation of synapse organization and synapse maturation. These differences might reflect a different maturational stage of the DG growing axons compared to the fibers from other hippocampal subregions. The results established in this work will be fundamental to further comprehend growth cones and their unique characteristics to achieve target specificity.

Disclosures: M. Krause: None. **K. Kronberg:** None. **G. Quattrocolo:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.03/A26

Topic: A.05. Axon and Dendrite Development

Support: BK21 Four (Fostering Outstanding Universities for Research)

Title: Selective expression of 3 ORs during early development of olfactory system and its link between GnRH neuron migration

Authors: *S. LEE, S. YOO;
Dept. of Life Sci., Hanyang Univ., Seoul, Korea, Republic of

Abstract: During early development, the olfactory placode(OP) generates a variety of cell types such as olfactory sensory neurons(OSN) and gonadotropin-releasing hormone(GnRH)--producing neurons. The GnRH neurons emerge in the OP area but they migrate into the hypothalamus during E11-E14. Kallmann syndrome, which is induced by disrupted migration of GnRH neurons, is characterized by impaired olfactory function and infertility, suggesting the existence of a link between the olfactory system and GnRH development. However, the precise interplay between the olfactory system and GnRH neuron migration is still enigmatic. Here we leverage single nucleus RNA-seq data which covers whole embryonic stages to resolve the cell type and molecular diversity during olfactory placode development. We identified an undiscovered population of olfactory sensory neurons characterized by their selective expression of specific odorant receptors(Olfr15, Olfr31, Olfr571) during E11-14, which is the same timepoint of GnRH neuron migration. Unlike other OSNs, these neurons express voltage-gated potassium channels and Prokinectin 2 receptor which is associated with GnRH neuron regulation. The DEGs of the population strikingly align with genes known as Kallmann syndrome's risk gene and axon guidance-related genes. In addition, they also show possability of Igf2-Igf1r cell to cell interactoin between pituitary gland progenitors with high communication probability. Our findings open a compelling avenue for further exploration, offering potential insight into the complex interplay between the olfactory system and reproductive neuroendocrinology.

Disclosures: S. Lee: None. **S. Yoo:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.04/A27

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant R15NS126957-01

Title: Spatiotemporal regulation of Robo1 expression by miR-219a in Slit-mediated axon repulsion

Authors: *B. KHOT[1], H. SURIYAARACHCHI[1], G. LIU[2];
[1]Biol., [2]Dept. of Biol. Sci., Univ. of Toledo, Toledo, OH

Abstract: Axon elongation and pathfinding are essential for forming proper neural circuits during development. Commissural axons in the developing vertebrate spinal cord differentially respond to the floor-plate derived chemorepellent Slits: inhibition of Slit repulsion in precrossing commissural axons and upregulation of Slit repulsion in postcrossing axons. It has been shown that differential expression of Robo1, a Slit repulsive receptor, in developing commissural neurons plays an important role in modulating Slit responsiveness to control commissural axon midline crossing. However, mechanisms differentially regulating Robo1 expression in developing commissural axons are not fully understood. Here, we show that the 3'UTR of Robo1 mRNA is regulated by miR-219a, a highly conserved miRNA, in a miRNA Response Element-dependent manner. Gga-miR-219a and cRobo1 protein are differentially expressed in the developing chicken spinal cord. Gga-miR-219a represses cRobo1 protein in commissural neurons through translation repression without affecting its mRNA levels. Either inhibition of miR-219a activities or expression of miR-219a-insensitive Robo1 in precrossing commissural neurons results in premature responsiveness to Slit repulsion. Disruption of the interactions between miR-219a and cRobo1 3'UTR causes commissural axon projection defects in the developing chicken spinal cord. These results suggest that suppression of Robo1 expression by miR-219a in developing commissural neurons regulates Slit sensitivity to facilitate commissural axon projection and midline crossing.

Disclosures: B. Khot: None. **H. Suriyaarachchi:** None. **G. Liu:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.05/A28

Topic: A.05. Axon and Dendrite Development

Support: NIH RF1AG083085
NIH DP1NS106665
NIH R01NS104055

Title: Molecular-subcellular mechanisms driving development of corticospinal circuitry, and potentially contributing to selective vulnerability of corticospinal circuits in ALS-FTD

Authors: *J. E. FROBERG;
Harvard Univ., Evanston, IL

Abstract: ALS/FTD centrally involve degeneration of function-specific subtypes of cortical subcerebral projection neurons (SCPN): in ALS, corticospinal neurons (CSN) controlling voluntary movement, and spinal motor neurons; in FTD, closely related von Economo neurons (VENs) and fork cells regulating emotion and cognition. Why these closely related neuronal subtypes are especially vulnerable in both ALS/FTD is unknown and likely key to

prevention/therapy, since in both patients carrying familial ALS/FTD mutations (e.g. SOD1, TDP-43, FUS, C9orf72), most neurons in brain and most body cells express the variant gene, but only specific neuronal subtypes degenerate. Molecular differences between affected subtypes and other even closely related neurons might render affected neurons more vulnerable to dysfunction from mis-expression/mutation. To identify potential molecular differences between subtypes, we performed a "multi-omic" investigation of RNA expression, translation efficiency, and protein abundance across multiple CSN subpopulations at multiple early, post-natal stages, and compared with similar data sets from unaffected callosal projection neurons (CPN) and corticothalamic projection neurons (CThPN). We observe, at "baseline", expression differences in multiple known ALS/FTD risk genes between CSN and unaffected subtypes early in their postnatal development in wild-type mice, potentially elucidating why mutation of these genes or other perturbations frequently lead to selective loss of CSN.
We also investigate whether subtype-specific subcellular localization of specific RNAs and proteins render corticospinal neurons (CSN) selectively vulnerable to degeneration in ALS by comparison of CSN presynaptic vs. soma molecular machinery in pre-onset hSOD1G93A vs. WT mice. Dysfunctional localization of molecules to CSN synapses might contribute to selective vulnerability of corticospinal circuitry in ALS. We have purified and quantitatively analyzed CSN synaptosomes, using optimized approaches for labeling and sorting subcellular material from specific subtypes, from CSN in WT and hSOD1G93A mice, and compare RNA abundances to identify mRNAs with altered axonal/synaptic localization as novel factors potentially contributing to vulnerability of corticospinal circuitry.

Disclosures: J.E. Froberg: None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.06/A29

Topic: A.05. Axon and Dendrite Development

Support: NIH R15 DC016407

Title: EphrinAs and EphAs are expressed in the embryonic and adult mouse gustatory systems and repel gustatory geniculate axons

Authors: M. AKSU[1], **R. JAISWAL**[1], A. GRUNDHOEFER[2], L. CHOYNA[1], P. THAKKAR[1], R. TREFFY[3], A. GEORGE[4], D. CHO[5], M. L. RUSSO[6], K. DOSHI[7], *M. W. ROCHLIN[8]; [1]Biol., Loyola Univ. Chicago, Chicago, IL; [2]Biol., Loyola U Chicago, Chicago, IL; [3]Neurosurg., Med. Col. of Wisconsin, Milwaukee, WI; [4]R&D Toxicology, AbbVie Inc., Lake Bluff, IL; [5]Psychiatry, Dell Med. Sch., Austin, TX; [6]Waisman Ctr., Madison, WI, ; [7]Intrnl. Med., Univ. of Massachusetts Mem. Hlth., Worcester, MA; [8]Biol., Loyola U. Chicago, Chicago, IL

Abstract: Ephs and ephrins are cell surface proteins that act as ligands and receptors for one another and typically mediate contact-dependent axon repulsion. EphrinAs are lipid-linked and interact primarily with EphAs, whereas ephrinBs are transmembrane and interact primarily with EphBs. In embryonic day 14.5 (E14.5) mouse tongue, when gustatory afferents have just entered fungiform papillae (FP) epithelium, in situ hybridization revealed that ephrinA1 and A3 are broadly distributed in the dorsal epithelium. At E16.5, epithelial ephrinA mRNA levels are higher than at E14.5. The FP epithelium and the papilla core tissue traversed by afferents exhibited lower levels of ephrinAs than surrounding epithelium at both stages. In E14.5 geniculate ganglia, EphA/ephrinA expression varies in intensity and location, with EphA5, A6, and A7 restricted to Phox2B+ (oral, mostly gustatory) neurons, and ephrinA2, A3, and A5 concentrated in Prrxl1+ neurons (aural somatosensory). In vitro, ephrinA-Fc's repel E18 rat geniculate and trigeminal neurites dose-dependently. Preliminary data indicate that E15.5 Phox2b-Cre::tdTomato mouse geniculate neurites (oral afferents) are also repelled by ephrinA stripes, and suggest that tdTomato-negative neurites were not as strongly repelled. In E15.5 Phox2b-Cre::tdTomato mice lacking ephrinA1, A3, and A4, gustatory axon arbors are larger than in wild type FP in the central region of the tongue. EphA/ephrinA expression is also evident in the adult geniculate ganglion and dorsal lingual epithelium and differs from embryonic expression. Geniculate ganglion sc-RNAseq data shows EphA5 expression continues to be elevated in taste transducing geniculate ganglion neurons. The variety of Ephs and ephrins expressed in the epithelium raises the possibility that Eph/ephrin signaling among dorsal lingual epithelial cells influences their migration and organization.

Disclosures: M. Aksu: None. **R. Jaiswal:** None. **A. Grundhoefer:** None. **L. Choyna:** None. **P. Thakkar:** None. **R. Treffy:** None. **A. George:** None. **D. Cho:** None. **M.L. Russo:** None. **K. Doshi:** None. **M.W. Rochlin:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.07/A30

Topic: A.05. Axon and Dendrite Development

Support: NSF BRC-BIO 2232510
IAS IASSG-S20-02

Title: 5-ht1a regulates axon outgrowth in a subpopulation of drosophila serotonergic neurons

Authors: A. KINSER, D. LONG, A. OLALDE-WELLING, L. BREWER, J. LIM, D. MATHENY, B. LONG, *D. ROOSSIEN;
Ball State Univ., Muncie, IN

Abstract: Serotonergic neurons produce extensively branched axons that fill most of the central nervous system, where they modulate a wide variety of behaviors. Proper behavioral output therefore depends on the precise outgrowth and targeting of serotonergic axons during development. To direct outgrowth, serotonergic neurons utilize serotonin as a signaling molecule prior to it assuming its neurotransmitter role. This process, termed serotonin autoregulation, regulates axon outgrowth, branching, and varicosity development of serotonergic neurons. However, the receptor that mediates serotonin autoregulation is unknown. Serotonin receptors are expressed either in non-serotonin producing neurons as heteroreceptors or in serotonergic neurons as autoreceptors. In non-serotonin producing neurons, serotonin receptor activity regulates neurite outgrowth and branching. Yet, there has not yet been a systematic test of the role of autoreceptor activity in the outgrowth of serotonergic axons. Here we asked if serotonin receptor 5-HT1A plays a role in serotonergic axon outgrowth and branching. Using cultured *Drosophila* serotonergic neurons, we found that exogenous serotonin reduced axon length and branching only in those expressing 5-HT1A. Pharmacological activation of 5-HT1A led to reduced axon length and branching, whereas disruption of 5-HT1A rescued outgrowth in the presence of exogenous serotonin. Altogether this suggests 5-HT1A is a serotonin autoreceptor in a subpopulation of serotonergic neurons and initiates signaling pathways that regulate axon outgrowth and branching during *Drosophila* development.

Disclosures: A. Kinser: None. **D. Long:** None. **A. Olalde-Welling:** None. **L. Brewer:** None. **J. Lim:** None. **D. Matheny:** None. **B. Long:** None. **D. Roossien:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.08/A31

Topic: A.05. Axon and Dendrite Development

Support: MIRA (R35)

Title: Actomyosin contractility in the formation and function of the axon initial segment

Authors: *J. TIDEI, J. BEACH, P. OAKES;
Loyola Univ. Chicago, Maywood, IL

Abstract: In addition to electrochemical and biochemical communication, neurons are also thought to communicate via mechanotransduction. Decades of research has established that neurons sense their mechanical environment during differentiation, pathfinding, and pathological perturbations, such as traumatic brain injury or plaque deposition. However, the molecular mechanism(s) by which mechanical cues are generated, sensed, and interpreted by neurons remain incomplete. Myosin 2 is the dominant contractile motor protein in cells, and individual myosin 2 monomers assemble into filaments that pull on the actin cytoskeleton to drive

contraction events. Consistent with recent literature, my preliminary data demonstrates a significant increase in active phosphorylated myosin 2 in a subcellular domain at the proximal base of axons, named the Axon Initial Segment (AIS). In addition to myosin, a mature AIS also contains the master scaffold protein Ankyrin-G that anchors voltage-gated ion channels, signaling proteins, and cell adhesion molecules to the neuronal cytoskeleton. Therefore, the AIS contains all the requisite components of adhesion-mediated mechanosensation: active actomyosin with transmembrane components that can couple the extracellular matrix to the intracellular cytoskeleton. The proximal spatial location of the AIS to the soma and nucleus makes it an opportune candidate for transducing mechanical cues into electrochemical and biochemical information that modulate neuronal decision making and behavior. We are currently using traction force microscopy (TFM) to characterize AIS mechanics. In addition, we hope to delineate the spatiotemporal regulation of myosin filament assembly more precisely in the AIS. Our overarching hypothesis is that actomyosin-generated contractility is critical for AIS maturation and neuronal mechanosensation.

Disclosures: J. Tidei: None. **J. Beach:** None. **P. Oakes:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.09/A32

Topic: A.05. Axon and Dendrite Development

Support: NSF-CRCNS award #2112862

Title: Brain serotonergic neurons in tunable hydrogels

Authors: *J. HAIMAN[1], S. JANUSONIS[4], N. ELYASI[5], M. AHUJA[2], E. LEDAKAITE[3]; [1]UC Santa Barbara, Santa Barbara, CA; [2]UC Santa Barbara, SAN JOSE, CA, ; [3]UC Santa Barbara, Isla Vista, CA, ; [4]Psychological and Brain Sci., Univ. of California Santa Barbara Neurosci., Santa Barbara, CA; [5]Univ. of California, Santa Barbara, SALINAS, CA.

Abstract: The self-organization of brain serotonergic axons (fibers), including its susceptibility to environmental perturbations, remains an unsolved problem in neuroscience. The formation of regional serotonergic fiber densities depends on stereotypic developmental sequences, a rich repertoire of transcriptional programs available to individual neurons, the strong stochasticity of many axonal paths, as well as on molecules that mediate axon adhesion and axon-axon interactions. In addition, serotonergic axons are almost unique in their capacity to regenerate in the adult mammalian brain. Direct manipulations of serotonergic axons and their environment are currently extremely challenging, which limits experimental and theoretical analyses. These analyses are important for fundamental neuroscience (serotonergic axons are present in high densities in the brains of all vertebrates, from the cartilaginous fishes to the mammals) and for

the understanding of several complex mental disorders (including major depressive disorder and autism spectrum disorder). In this study, we used primary brainstem neurons from transgenic mice (Tph2-EYFP) to produce serotonergic cell cultures in 3D-hydrogels with tunable viscoelastic properties. The storage and loss moduli of the hydrogels were informed by experimental measurements in the mouse brainstem. The morphology and other properties of the neurons were visualized with immunocytochemistry for serotonergic and other markers, imaged with confocal microscopy, and analyzed in 3D in Imaris (Bitplane). Hydrogel-based cultures of serotonergic neurons can support a wide range of studies into normal and perturbed serotonergic signaling.

Disclosures: J. Haiman: None. **S. Janusonis:** None. **N. Elyasi:** None. **M. Ahuja:** None. **E. Ledakaite:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.10/A33

Topic: A.05. Axon and Dendrite Development

Support: SAMSUNG Grant, SEFC-MA2302-05

Title: Investigating Kctd3's function in regulating DAAM1 during neurite growth and axon initial segment formation

Authors: *Y. OH, Y. CHO;
DGIST, Daegu, Korea, Republic of

Abstract: Kctd3 is associated with human neurodevelopmental disorders, featuring epileptic encephalopathy and global developmental delay. However, the precise molecular mechanisms remain elusive. Employing a Kctd3 knockout mouse model and knockdown models, we elucidated the impact of Kctd3 on neuronal development and morphogenesis. Our findings reveal that Kctd3 depletion leads to reduced levels of DAAM1 protein, resulting in impaired neurite growth and reduced growth cone size in both peripheral and central nervous systems. Additionally, abnormal distribution of Ankyrin G suggests inhibited axonal growth due to impaired assembly of axon initial segments in Kctd3-deficient conditions. Importantly, we showed Daam1 can rescue the deficits observed in Kctd3-deficient conditions, suggesting their hierarchical relationship. Moreover, diaphragm muscle NMJ innervation in Kctd3 knockdown mice showed a decrease compared to controls, indicating a potential role of Kctd3 in neuromuscular junction development. Sciatic nerve injury in Kctd3 knockdown mice resulted in slight deterioration of EHL muscle NMJ innervation by day 13 post-injury. These results underscore the significance of Kctd3 in connecting neuronal and muscular systems. Notably, we hypothesize a potential link between abnormal Ankyrin G distribution and synapse formation

with target, shedding light on additional avenues for investigation into Kctd3's role in synaptic development and function. Our study provides insights into the molecular mechanisms underlying Kctd3's functional relationship with Daam1, offering potential therapeutic targets for alleviating symptoms associated with Kctd3-related disorders. Further investigation into the interaction between Kctd3 and Daam1 is needed to enhance our understanding and treatment options for these diseases.

Disclosures: Y. Oh: None. **Y. Cho:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.11/A34

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant R01EY031690
Knights Templar Eye Foundation Career Starter Grant

Title: Role of clustered Protocadherins in retinal ganglion cell axon morphology

Authors: *S. SON[1], C. MCLEOD[2], S. BHANDARI[2], M. AKPO[3], A. M. GARRETT[2,4]; [1]Wayne State Univ., Detroit, MI; [2]Pharmacol., Wayne State Univ., Detroit, MI; [3]Ophthalmology, Visual, and Anatom. Sci., Wayne State Univ., Detroit, MI; [4]Ophthalmology, Visual, and Anatomical Sciences, Wayne State University, Detroit, MI

Abstract: Clustered protocadherins (cPcdhs, comprised of the α, β, and γ-Pcdhs) have garnered significant attention for their isoform diversity giving each neuron a unique identity essential for neural development and circuit formation. Here, we use a mouse model lacking all isoforms except γC4 (*Pcdhg-1R1*) – which has normal neuronal cell number but disrupted starburst amacrine cell (SAC) self-avoidance – to explore the role of cPcdhs in retinal ganglion cell (RGC) axon phenotype independent of cell death. To analyze the combined effects of α- and γ-Pcdhs, we use AAV vectors with shRNA constructs to knock down the *Pcdha* cluster in *Pcdhg-1R1* mutants. In these animals, we observed that axon terminals of RGCs were densely clustered in lateral geniculate nucleus (LGN). To clarify the subtype-specific axon terminal morphology, we focus on a particular type of RGC using the synthetic promoter ProD1. ProD1-mediated expression is limited to a subset of ON-OFF direction-selective ganglion cells (ooDSGCs), bistratified ganglion cells whose dendrites align with those of SACs and express the marker CART. To visualize individual neurons, we co-injected AAV vectors encoding ProD1 Cre along with Brainbow vectors (AAV-EF1a-BbChT and AAV-EF1a-BbTagBY), which allow the visualization of 8 distinct colors, into the eyes of *Pcdhg-1R1* and C57 mice. All the axon terminals of ProD1-driven RGCs in the LGN were found to colocalize with vesicular glutamate transporter 2 (VGLUT2), a presynaptic marker for RGCs. In *Pcdhg-1R1* mice, we observed

clusters of 6-7 boutons in the dLGN. With the additional knockdown of the *Pcdha* cluster, we noticed defects in the dendrite arborization of RGCs in the retina and more severe clustering of axon terminals in the dLGN. Ongoing work aims to define how impaired function in RGCs affect their synaptic connectivity from the retina to the thalamus using WGA (wheatgerm agglutinin). This work will shed light on the mechanisms underlying visual processing abnormalities associated with RGC dysfunction.

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

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.12/A35

Topic: A.05. Axon and Dendrite Development

Support: NIH Pioneer Award DP1 NSI06665
Travis Roy Foundation
NIH T32AG000222
NIH F30HD113352
Fondation Jean-Jacques et Felicia Lopez-Loreta pour excellence académique
HCBI Simmons Award
NIH MSTP T32GM007753

Title: Dynamic regulation of subcellular molecular machinery of corticospinal growth cones across developmental stages of circuit development

Authors: *M. A. VICENT, A. ENGMANN, P. NANDA, J. FROBERG, O. DURAK, D. NGUYEN, J. D. MACKLIS;
Harvard Univ., Cambridge, MA

Abstract: Corticospinal neurons (CSN) are central for fine motor control. Their cell bodies are located in layer V of neocortex. During development, CSN extend their axonal projections over remarkably long distances to the brainstem and spinal cord, establishing exquisitely precise functional circuitry. Injury or degeneration of CSN circuitry causes critical and irreversible loss of motor function in spinal cord injury and motor neuron diseases. Over the past two decades, deep investigation of neuronal subtype-specific soma transcriptomes has provided substantial insight into the “molecular logic” of CSN subtype specification and diversity through early-mid corticogenesis. However, knowledge of molecular mechanisms controlling subsequent aspects of development - such as CSN axon elongation, grey matter innervation, branching and collateralization, synapse formation, and functional circuit maturation - is still limited. Recent

work has revealed that neurons contain multiple distinct subcellular transcriptomes, and that local protein synthesis of axonally-enriched transcripts is required for directional responses to at least some guidance cues, and for formation of presynaptic terminals. However, the composition of subtype-specific growth cone (GC)-localized molecular machinery and the dynamic regulation of these subcellular processes across distinct stages of circuit formation are essentially unknown. We apply a combination of neuronal subtype-specific labeling, biochemical fractionation, and fluorescent small particle sorting to purify CSN-specific GCs and corresponding parent somata directly from mouse CNS. This enables investigation of dynamic changes in subcellular CSN soma vs. GC transcriptomes in response to changing, complex, *in-vivo* environments across distinct stages of circuit formation in the first postnatal week. Subcellular mapping of transcripts, and analysis of differential changes across developmental stages, identifies subsets of GC-localized transcripts and potential regulatory mechanisms for RNA trafficking, stability, and local translation likely centrally involved in local implementation of CSN circuitry. Increasingly deep knowledge of molecular processes that enable successful and specific CSN circuit development promises to also deepen understanding of mechanisms of degeneration or failed regeneration following injury, and to potentially enable new therapeutic approaches.

Disclosures: M.A. Vicent: None. **A. Engmann:** None. **P. Nanda:** None. **J. Froberg:** None. **O. Durak:** None. **D. Nguyen:** None. **J.D. Macklis:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.13/A36

Topic: A.05. Axon and Dendrite Development

Support: NIH Pioneer Award DP1 NS106665
NIH Grant R01 NS045523

Title: Investigation of cortical projection neurons of distinct circuits reveals subtype-specific protein compositions of ribosomes

Authors: *T. TRAN[1], J. FROBERG[2], J. D. MACKLIS[3];
[2]Stem Cell and Regenerative Biol., [3]Dept of Stem Cell and Regenerative Biology, and Ctr. for Brain Sci., [1]Harvard Univ., Cambridge, MA

Abstract: In the mammalian cerebral cortex, diverse subtypes of projection neurons (PN) form extremely long-range axonal connections to their distinct targets, and are responsible for motor, sensory, cognitive, and behavioral functions. During development, PN form growth cones, subcellular specializations that locally integrate environmental cues and direct axonal pathfinding and synapse formation semi-autonomously. These processes are likely controlled at least partly by local subcellular translational regulation. However, the extent to which

translational regulation is specialized for distinct cortical PN subtypes to implement circuit-specific axon guidance remains essentially uninvestigated, and subtype-specific molecular regulators over such regulation have not been identified from cortical PN *in vivo*. Meanwhile, increasing evidence implicates the role of ribosomes in neuronal biology; while other studies highlight the vast potential for specialization of ribosomes' function via modifying their protein composition of ribosomal proteins (RPs) and associated protein (RAPs). These observations motivate us to investigate the hypothesis that ribosomes might have distinct protein compositions in distinct cortical PN, which might enable specialized subtype-specific local translational control that regulates nervous system circuit development. To address this hypothesis, we use a combination of retrograde labeling of circuit-specific somata for neuronal fluorescence-activated cell sorting, and ribosome immunoprecipitation and mass spectrometry (IP-MS) to investigate the protein composition of ribosomes recovered from low, practical numbers of subtype-specific cortical PN. We developed two approaches that target different epitopes of the ribosome, focusing first on 100,000 callosal PN (CPN; send their axons via the corpus callosum axonal tract linking the two cortical hemispheres). Using the approach that targets ribosomal RNA for endogenous ribosome IP-MS, we then conducted a comparative analysis between CPN and subcerebral PN (SCPN), the entire population that projects from the cortex to the brainstem and spinal cord, two exemplar subtypes with distinct circuits. Proteomic analysis reveals that RPS30 is enriched in CPN ribosomes, while ribosomes of both subtypes share largely the same RP composition. Intriguingly, we identify several RAPs that are preferentially enriched in SCPN ribosomes to the point of not being detectable in CPN ribosomes. We are working on immunocytochemistry experiments to validate the subtype-specific enrichment in CPN and SCN ribosomes of select candidate proteins.

Disclosures: T. Tran: None. **J. Froberg:** None. **J.D. Macklis:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.14/A37

Topic: A.05. Axon and Dendrite Development

Support: R01-EY029739

Title: An extracellular matrix derived recombinant protein promotes retinal ganglion cell survival and axon regeneration after optic nerve injury in vivo

Authors: *M. FROST;
UConn Hlth., Farmington, CT

Abstract: Retinal ganglion cells (RGCs) are central nervous system (CNS) projection neurons that are responsible for the transmission of visual information from the retina, through the optic

nerve, chiasm, and tract to reach its associated brain targets. Like all CNS projection neurons, RGCs fail to regenerate their axons after injury resulting in permanent disability and loss of vision following disease or injury. Unfortunately, there are no clinically available treatments that can promote CNS axon regeneration to restore CNS function. Therefore, to overcome this unmet clinical need, we have identified a component of the extracellular matrix that promotes long-distance RGC regeneration in the optic nerve. Through bioinformatic analysis of RGCs by single cell RNA sequencing we were able to predict extracellular matrix proteins that could interact with RGCs axons and regulate their ability to grow and regenerate. We tested if these molecules could promote axon regeneration of RGCs following optic nerve crush (ONC) injury. We determined that one of these molecules increased RGC survival following injury and promoted long-distance axon regeneration. Next, we synthesized a recombinant variant of this molecule, and found that its targeted delivery promoted axon regeneration after optic nerve cush injury in vivo. This recombinant molecule derived from an extracellular matrix, presents as a novel CNS neuroprotectant and axon regenerating potential therapeutic. Finally, we wanted to determine whether the immune stimulating treatment zymosan, which promotes axon regeneration, increased the amount of this extracellular matrix molecule. We determined that zymosan stimulation of inflammation substantially increased the amount of this extra-axonal molecule compared to our control conditions through the increased infiltration of macrophages.

Disclosures: M. Frost: None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.15/A38

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant IOS-1846234-003

Title: Comparative developmental proteomics modulatory and excitatory axons converging on the striatum

Authors: *M. MASOTTI[1], V. DUMRONGPRECHACHAN[1], M. L. MACDONALD[2], Y. KOZOROVITSKIY[3];
[1]Northwestern Univ., Evanston, IL; [2]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [3]Neurobio., Northwestern Univ., Evanston, IL

Abstract: The basal ganglia are a set of midbrain structures critical for goal-directed movement and reward-based behavior. Information from mid-brain dopamine, thalamic, and cortical regions converges on the striatum, the primary input region of the basal ganglia. These incoming signals are important regulators of striatal synapse genesis. The development of axons innervating the striatum is a dynamic process occurring in utero and early in the postnatal period.

During this time, changes in the proteome of axonal growth cones are required for correct axonal targeting and maturation, as well as synapse development. Despite this fundamental need for precise coordination of local protein synthesis, signaling, and degradation, not much is known about the developmental proteome of axons. This is due, in part, to the challenge of tracking the proteins within specific populations of axons with requite precision and depth. Here, we use a new genetically targeted APEX peroxidase reporter mouse line we have generated to achieve cell-specific labeling of cortical and dopaminergic axons innervating the striatum. Using this method, we aim to identify, quantify, and track axon-enriched proteins in distinct neuronal populations from neonatal to young adult age. Identified axonal proteins could be organized into clusters displaying distinctive developmental trajectories, where several clusters were enriched in neuropsychiatric risk genes. Further, this work allows for the comparison of two distinct axon classes, a vital comparison because dopaminergic modulation guides activity and glutamate release-dependent striatal synapse formation. How axons from distal sites collaboratively drive synaptogenesis and coordinate their protein expression over time in the target region is unknown. This work will provide insight into two key presynaptic proteomes during a period of rapid striatal synapse maturation essential for basal ganglia function and dysfunction in neuropsychiatric diseases.

Disclosures: M. Masotti: None. **V. Dumrongprechachan:** None. **M.L. MacDonald:** None. **Y. Kozorovitskiy:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.16/A39

Topic: A.05. Axon and Dendrite Development

Support: NIH R01 NS107456

Title: Palmitoylation of the p75 neurotrophin receptor is required for its retrograde degenerative signaling in sympathetic neurons

Authors: A. PATHAK[1], ***H. DAS**[2], A. SPANO[3], C. DEPPMANN[3], B. D. CARTER[4]; [1]Biochem. Dept., Vanderbilt Univ. Med. Res. Ctr., Nashville, TN; [2]Vanderbilt Univ., Nashville, TN; [3]Univ. of Virginia, Charlottesville, VA, VA; [4]Dept. of Biochem. Vanderbilt Brain Inst., Vanderbilt Univ. Med. Sch., Nashville, TN

Abstract: During development, neurotrophins can activate retrograde, long-range, pro-survival signaling by forming Trk receptor “signaling endosomes” (SEs) in distal axons. Similarly, we recently found that activation of the p75 neurotrophin receptor (p75NTR) in distal axons, by trophic factor deprivation or pro-apoptotic ligand binding, initiates a retrograde, degenerative signal involving the intracellular domain (ICD) fragment of p75NTR. However, the mechanisms

for biogenesis and transport of such a degenerative signaling endosomes (DSEs) is not known. Here, we demonstrate that palmitoylation of p75NTR at a highly conserved, juxtamembrane cysteine residue (279 in rat) is required for the formation of DSEs and retrograde apoptotic signaling. Mutation of cysteine 279 to alanine in p75NTR significantly inhibited ligand-induced receptor internalization diminishing the formation of p75NTR ICD axonal puncta and completely abrogated retrograde apoptotic signaling, when introduced into p75-/- sympathetic neurons. Similarly, addition of the palmitoylation inhibitor, 2-bromopalmitate, to distal axons also blocked the generation of axonal ICD puncta and retrograde apoptosis induced by p75NTR activation in distal axons. To explore the role of p75NTR palmitoylation *in vivo*, we generated mice carrying a C281A mutation in p75NTR. We found that mutant postnatal day 0 mice exhibited a substantial reduction in neuronal apoptosis in the superior cervical ganglia (SCG), with wild type having an average of 21 $\pm$ 3 cleaved caspase 3+ (CC3) neurons/SCG, while p75-/- mice had 2.5 $\pm$ 0.5 CC3+ neurons/SCG and mice homozygous for C281A had 6.3 $\pm$ 1.85 CC3+ neurons/SCG. Together, these findings suggest that palmitoylation of p75NTR is essential for the biogenesis of DSEs and normal, developmental apoptosis of these neurons.

Disclosures: A. Pathak: None. **H. Das:** None. **A. Spano:** None. **C. Deppmann:** None. **B.D. Carter:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.17/A40

Topic: A.05. Axon and Dendrite Development

Support: R01 MH119346 (RJG)
Adelson Medical Research Foundation (ALB, MNR, RJG)

Title: Plexina2 and ncam collaborate to direct hippocampal mossy fiber development and laminar patterning

Authors: *X.-F. ZHAO[1], R. KOHEN[2], Y. ZENG[2], X. ZHANG[2], B. C. LIM[4], J. A. OSES-PRIETO[5], J. M. RASBAND[4], A. L. BURLINGAME[5], M. N. RASBAND[4], R. J. GIGER[2,3]; [1]Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [2]Cell and Developmental Biol., [3]Neurol., Univ. of Michigan, Ann Arbor, MI; [4]Neurosci., Baylor Col. of Med., Houston, TX; [5]Univ. of California San Francisco, San Francisco, CA

Abstract: Proper functioning of the nervous system depends on the precise wiring of neural circuits. Axonal pathfinding is achieved through the incremental elongation of axons and the navigation of growth cones through intermediate targets until they reach their final targets, where synapses are formed. In this study, we investigated the role of Sema6 and class A Plexin (PlxnA) family members in guiding and patterning developing hippocampal mossy fibers (MF) in the

mouse forebrain. By conditionally deleting *Sema6a* and *Plxna2* in neurons and disrupting the GTPase-activating protein (GAP) activity of PlxnA2, we demonstrate that both GAP-dependent and GAP-independent guidance mechanisms direct MF axons at distinct choice points. To explore the molecular interactions involving PlxnA2-mediated guidance events, we employed antibody-directed proximity biotinylation of primary hippocampal neurons followed by proteomics. In addition to PlxnA2 and PlxnA4, we identified several members of the Ig-CAM family, including NCAM. NCAM is of interest because previous work reported its role in MF patterning. Moreover, genome-wide association studies indicate that mutations in PLXNA2, SEMA6A, and NCAM1 may contribute to neuropsychiatric illness. Our mechanistic studies revealed a genetic interaction between *Plxna2* and *Ncam1* for the separation of MF into suprapyramidal and infrapyramidal axon bundles in CA3b/c. Furthermore, we discovered that MF laminar targeting to the stratum radiatum and oriens in CA3a, and the regulation of the length of infrapyramidal axons, rely on the neuronal expression of *Plxna2*, *Sema6a*, and *Ncam1*. Overall, our work provides insights into the multifaceted functions of the PlxnA2 receptor complex in the development of the DG-CA3 system, a brain structure crucial for brain health.

Disclosures: X. Zhao: None. **R. Kohen:** None. **Y. zeng:** None. **X. Zhang:** None. **B.C. Lim:** None. **J.A. Oses-Prieto:** None. **J.M. Rasband:** None. **A.L. Burlingame:** None. **M.N. Rasband:** None. **R.J. Giger:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.18/A41

Topic: A.05. Axon and Dendrite Development

Support: NIH intramural program grant 1ZIANS003140-08

Title: A local CRMP2-Trio signaling axis for repulsive axon guidance

Authors: *E. FINGLETON;
NINDS, NIH, Bethesda, MD

Abstract: Trio is a neuronal Rho Guanosine nucleotide Exchange Factor (GEF) critical for neurodevelopment; mutations affecting Trio GEF function are associated with autosomal dominant intellectual developmental disorders (MRD63 and MRD44). Trio is a cytoskeletal remodeler in various contexts including axon patterning and structural plasticity at the synapse. How is Trio recruited to these locales and activated at appropriate times? Via immunoprecipitation/mass spectrometry, we identified CRMP2 as a major Trio-interactor across developmental time points (embryonic, perinatal, post-weaning, adulthood). We further observed a preferential interaction between Trio and phospho-CRMP2 (pCRMP2), which is known to mediate repulsive axon guidance signaling events. We hypothesized Trio may mediate pCRMP2

signaling in the axon, and indeed Trio knock-down reverses axon branching phenotypes downstream of CRMP2 phosphomutant over-expression. Additionally we find that Trio and pCRMP2 are required in the same pathway downstream of Semaphorin3A (Sema3A), a repulsive axon guidance cue that requires pCRMP2. We are currently investigating whether a similar Trio-CRMP2 signaling axis is invoked downstream of other axon guidance cues and at other cellular locales, such as the synapse. We are additionally investigating if CRMP2-dependent processes are disrupted in a mouse model of Trio hyperfunction. Besides contributing to our understanding of how extracellular signals are translated into cytoskeletal phenotypes, these findings will supplement our understanding of Trio-related developmental delay. This work is funded by the NIH Intramural Research Program under grant 1ZIANS003140-08

Disclosures: E. Fingleton: None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.19/A42

Topic: A.05. Axon and Dendrite Development

Title: Investigating the importance of beta-spectrin for neuronal integrity

Authors: *D. GARCIA, C. DAVISON, M. HAMMARLUND;
Dept. of Neurosci., Yale Univ., New Haven, CT

Abstract: The neuronal cytoskeleton maintains the structural integrity of neurons and is required for axon formation and axonal transport. Spectrins, key components of the neuronal cytoskeleton, are scaffolding proteins that form heterodimers of α and β subunits to maintain plasma membrane integrity and overall structure of the cytoskeleton. In C. elegans, unc-70 is the only gene that encodes β-spectrin. Complete loss of unc-70 in C. elegans causes spontaneous axon breakage in the VD/DD GABAergic motor neurons. However, whether unc-70 is required within the neurons themselves or as a scaffold in the surrounding hypodermal tissue to maintain axonal integrity is controversial.
We hypothesized that unc-70 acts intrinsically within neurons to maintain axonal integrity. To investigate the importance of unc-70 /β-spectrin within neurons for axonal integrity, we used the auxin-inducible degradation (AID) system. The AID system allows us to rapidly deplete the UNC-70 protein in a tissue- and time-specific manner. We found degradation of UNC-70 only in neurons resulted in spontaneous axon breakage of the VD/DD neurons. In young animals we observed robust axon regeneration as a consequence of breakage, with many axons extending growth cones and attempting to repair the damage. To remove confounding effects of axon regeneration, we assessed axon damage after unc-70 neuronal AID in dlk-1 mutants, which are unable to regenerate. We found that 100% of axons are broken in these animals. These results indicate that unc-70 acts cell intrinsically to protect the integrity of VD/DD axons. Interestingly,

we observed that not all neuron types broke when UNC-70 was degraded. The touch receptor neurons ALM and PLM were not damaged by loss of UNC-70 from all neurons.
My ongoing experiments aim to further characterize the cell-intrinsic importance of unc-70 in VD/DD GABA neurons by degrading UNC-70/ β-spectrin only in GABA neurons, determining the timing of degradation required for axons to break in various ages, and characterizing breakage phenotypes in numerous neuron types including the touch receptor and cholinergic neurons. Overall, this research will help us understand the importance of spectrin and the axonal cytoskeleton to maintain neuronal integrity.

Disclosures: D. Garcia: None. **C. Davison:** None. **M. Hammarlund:** None.

Poster

PSTR318: Molecular and Cellular Mechanisms Regulating Axon Development and Neural Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR318.20/A43

Topic: A.05. Axon and Dendrite Development

Support: CIHR

Title: The involvement of VLK in retinal ganglion cell polarity

Authors: *X. CHEN[1,2], H. HARADA[3], P. P. MONNIER[4,5];
[1]Dept. of Physiol., Univ. of Toronto, TORONTO, ON, Canada; [2]Donald K. Johnson Eye Institute, University Health Network, Toronto, ON, Canada; [3]Donald K. Johnson Eye Inst., Univ. Hlth. Network, Toronto, ON, Canada; [4]Toronto Western Res. Inst., Toronto, ON, Canada; [5]Department of Physiology, University of Toronto, Toronto, ON, Canada

Abstract: Neuronal polarity refers to the asymmetrical distribution of cellular components within a neuron. A defect in neuronal polarity results in dramatic neurological conditions and has been observed in both developmental and neurodegenerative disorders such as autism, ADHD, Alzheimer's, and Parkinson's. Despite the fundamental importance of neuronal polarity, our understanding of the molecular mechanisms governing this process remains very limited. Retinal ganglion cells (RGC) serve a critical role in propagating visual stimulus from the retina to the brain, RGCs are highly polarized, they extend axons to the optic nerve layer, and communicate to the brain, and arborize dendrites into inner plexiform layers to receive inputs from amacrine cells and bipolar cells. However, there is very little known about RGC polarity formation. Vertebrate lonesome kinase (VLK) is an extracellular kinase that plays a critical role during axon guidance, lung development, and skeletal formation.(Brütsch et al., 2023; Harada et al., 2019; Probst et al., 2013) Since VLK global knockout in mice is embryonically lethal, we generated a VLK conditional knockout (cKO) animal model that allows for VLK deletion in the developing retina: by using the DKK3-Cre which only shows Cre recombinase activity in most retinal progenitors from early stages to cross with VLK flox animals(Sato et al., 2007). To visualize the

axonal outgrowth of RGC in these mice, the Thy1-YFPH line is used which only labels 1% of RGC in the retina, allowing us to study the axon and dendrite pattern from individual RGCs(Feng et al., 2000). We discovered that in VLK cKO animals display defects in RGC polarity, 49% of VLK cKO animals have Thy1 positive RGCs show axons extend on the same side as dendrites from the apical side of RGC, compared to only 4.9% in control animals. The optical coherence tomography test shows the retina thickness of VLK cKO animals is only half as thick as that of the control animals. Since neurons' shape determines function, optokinetic optometry is performed to study the visual acuity of these animals. 53.8% of the animals also show strongly impaired vision in the optometry test. Together these findings suggest the new critical role of extracellular kinase VLK in RGC polarity establishment and visual function.

Disclosures: X. Chen: None. **H. Harada:** None. **P.P. Monnier:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR319.01/A44

Topic: A.07. Developmental Disorders

Support: NIH Grant HD084289

Title: Acute fluoxetine treatment differentially affects behavioral flexibility and repetitive motor behaviors in female and male Fmr1 knockout mice

Authors: *K. G. AMODEO, V. MURILLO, M. E. RAGOZZINO;
Psychology, Univ. of Illinois Chicago, Chicago, IL

Abstract: Fragile X syndrome (FXS) is an intellectual disability caused by mutation of the Fragile X Messenger Ribonucleoprotein (FMR1) gene on the X chromosome. Individuals with FXS commonly exhibit learning disabilities, anxiety, behavioral inflexibility, repetitive motor behaviors and hyperactivity. Currently, there are limited treatments to reduce the core symptoms in FXS. Past studies indicate that some individuals with FXS may have enhanced serotonin reuptake which may contribute to core symptoms. Thus, treatment with a selective serotonin reuptake inhibitors (SSRI) may reduce certain symptoms in FXS. The present study investigated whether acute treatment with the SSRI, fluoxetine affects behavioral flexibility, stereotyped motor behavior, anxiety or hyperactivity in male and female Fmr1 knockout (KO) mice. An open field conflict test was used to investigate behavioral flexibility in which a mouse must inhibit a prepotent response to avoid an open center area to receive food rewards. Initial findings indicate that fluoxetine at 3 mg/kg significantly improves behavioral flexibility in female Fmr1 KO and wildtype (WT) mice by decreasing the latency to eat food rewards and time spent in the center area compared to that of saline treatment. However, preliminary results suggest the same treatment does not affect behavioral flexibility in male Fmr1 KO or WT mice. In the nesting removal test, mice exhibit increased digging of bedding material with removal of nesting

material. Fluoxetine treatment at 3 mg/kg and 10 mg/kg significantly reduced elevated digging behavior in female Fmr1 KO mice, but not male Fmr1 KO mice. Fluoxetine at 3 mg/kg or 10 mg/kg significantly decreased elevated digging behavior in male and female WT mice. In contrast, acute fluoxetine treatment did not affect anxiety-like behavior as measured in the zero maze or hyperactivity observed in multiple tests. Taken together, the initial results suggest that acute treatment with a SSRI may improve behavioral flexibility and reduce repetitive motor behaviors in females with FXS, but not males. Ongoing studies are investigating whether chronic treatment with a SSRI affects behavioral flexibility and repetitive motor behaviors in male and female Fmr1 KO mice.

Disclosures: K.G. Amodeo: None. **V. Murillo:** None. **M.E. Ragozzino:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR319.02/A45

Topic: A.07. Developmental Disorders

Support: Knights Templar Eye Foundation Career Starter Award
Northwestern Summer Undergraduate Research Grant
Northwestern Summer Undergraduate Internship Grant Program
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NIH R01EY030565

Title: Atypical retinal function in a mouse model of Fragile X syndrome

Authors: *A. L. VLASITS[1], M. SYEDA[2], A. WICKMAN[2], P. GUZMAN[2], T. M. SCHMIDT[2]; [1]Univ. of Illinois, Chicago, Chicago, IL; [2]Neurobio., Northwestern Univ., Evanston, IL

Abstract: In Fragile X syndrome and other autism-related disorders, many brain areas exhibit changes in circuit function manifesting as increases in excitatory-inhibitory (E-I) balance. Whether these neurodevelopmental disorders lead to similar changes in neural circuitry within the retina is not known. Humans with Fragile X syndrome and mouse models both exhibit signs of atypical vision, including lower contrast sensitivity and lower b-wave amplitudes of the electroretinogram, suggesting that retinal processing may not develop typically. We explored retinal function in the Fmr1 knockout model of Fragile X syndrome, focusing on a specific type of retinal neuron, the “sustained On alpha” retinal ganglion cell. We found that these cells exhibit changes in dendritic structure and dampened responses to light in the Fmr1 knockout. We show that decreased light sensitivity is due to increased inhibitory input and reduced E-I balance. The change in E-I balance supports maintenance of circuit excitability similar to what has been observed in cortex. These results show that loss of Fmr1 in the mouse retina affects sensory function of one retinal neuron type. Our findings suggest that the retina may be relevant for understanding visual function in Fragile X syndrome.

Disclosures: A.L. Vlasits: None. **M. Syeda:** None. **A. Wickman:** None. **P. Guzman:** None. **T.M. Schmidt:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR319.03/A46

Topic: A.07. Developmental Disorders

Support: R01NS117597 (NIH-NINDS),
R01HD054453 (NIH-NICHD)
Department of Defense (DOD, 13196175)
the Center for Autism Research and Treatment at UCLA

Title: Cell specific transcriptomic analysis in Fmr1 knockout mice identifies EPAC2 as a potential therapeutic target for Fragile X Syndrome.

Authors: *A. SURESH[1], J. E. BUTH[2], M. J. GANDAL[3], C. PORTERA-CAILLIAU[4];
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Abstract: Fragile X Syndrome (FXS) is a prototypical neurodevelopmental condition characterized by intellectual disability, autistic traits, and atypical sensory processing. It is caused by transcriptional silencing of the *FMR1* gene, which leads to the near complete loss of fragile X messenger ribonucleoprotein (FMRP), an RNA binding protein that functions as a translational suppressor of several hundred proteins. Exactly how loss of FMRP and the resulting dysregulation of molecular signaling pathways affects brain circuit function remains an area of active investigation. To date, it has been particularly difficult to link FMRP with molecular signaling pathways that regulate synaptic strength and dendritic spine turnover, both of which are affected in *Fmr1* knockout (KO) mice, the principal animal model of FXS. In parallel, other efforts have implicated changes in excitatory and inhibitory circuits in the etiology of FXS, including reduced firing and density of parvalbumin (PV) neurons, the major subtype of inhibitory interneurons in the cerebral cortex. To investigate whether loss of FMRP similarly affects the transcriptome of excitatory and inhibitory neurons, we used a Ribo-Tag approach to isolate mRNA specifically from Ca^{2+}/calmodulin-dependent protein kinase II (CAMK2) and PV neurons in primary somatosensory (S1) and visual (V1) cortices of adult *Fmr1 KO* mice and wild-type (WT) controls. This revealed hundreds of differentially expressed (DE) between *Fmr1* KO and WT mice, especially in excitatory neurons, but without clear region-specific differences. Intersectional analysis identified 194 DE genes that were shared between both CAMK2 and PV neurons, including several autism risk genes and genes known to be regulated by FMRP. Gene enrichment analysis of the shared genes identified pathways enriched for GTPase signal transduction and Golgi organization. Among these shared genes, we identified *Epac2* (a.k.a.,

Rapgef4), a cAMP dependent guanine-exchange factor, as the only DE gene (upregulated in *Fmr1* KO mice) that is also an autism risk gene, a target of FMRP, and highly enriched in brain tissue. Overactivation of EPAC2 is known to induce spine shrinkage and turnover, as well as lower GLUA2 AMPA receptor content. Strikingly, our group and others have reported similar synaptic phenotypes in *Fmr1* KO mice. We therefore used a pharmacologic approach to inhibit EPAC2 in *Fmr1* KO mice. We found that chronic administration of ESI-05, a specific EPAC2 antagonist, rescued tactile defensiveness in *Fmr1* KO mice in response to repetitive aversive whisker stimulation. These studies identify EPAC2 as a potential therapeutic target for FXS.

Disclosures: A. Suresh: None. **J.E. Buth:** None. **M.J. Gandal:** None. **C. Portera-Cailliau:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

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Program #/Poster #: PSTR319.04/A47

Topic: A.07. Developmental Disorders

Support: R01NS109381
HT9425-23-ARP-IDA

Title: The role of astrocytes in deficient sleep in Fragile X syndrome mouse model

Authors: A. ANDING[1], P. RAGUNATHAN[2], P. ZHONG[3], *A. DUNAEVSKY[4];
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Abstract: Clinical polysomnography studies show that children with Fragile X syndrome (FXS) suffer rapid-eye movement (REM) sleep deficiency. The consequences of sleep deprivation have negative effects on cognition, emotional processing, and several aspects of physical health and overall quality of life, but the mechanisms of REM sleep deficiency in FXS are not fully understood. Neurons are the most commonly targeted cell type in FXS studies. However, the activity of astrocytes has also been implicated in sleep regulation. Further, our lab and others have shown that astrocytes display an abnormal increase in cytosolic calcium (Ca^{2+}) signaling in the *Fmr1* KO mouse, a model of FXS. We performed simultaneous cortical electroencephalography (EEG), electromyography (EMG) recordings and behavioral monitoring in *Fmr1* KO and astrocyte-deleted cKO mice using telemetry devices to examine electrophysiological architecture associated with sleep and wake cycles in FXS, and determine the role of astrocytes in mediating sleep impairments. Recordings were collected from adolescence (2 months) to adulthood (5 months) to examine sleep architecture across development. We found that at 5 months of age *Fmr1* KO mice exhibit decreased sleep during the light phase. The reduced sleep in the *Fmr1* KO mice is observed both during REM and non-

REM (NREM) sleep. To isolate the effect of astrocytic FMRP on sleep impairments, we used the Aldh1l1-cre ERT2 line for conditional deletion in astrocytes (*Fmr1* cKO) and compared to littermate controls. Preliminary data indicate reduced sleep in the *Fmr1* cKO mice at 5 month of age. In ongoing experiments, we are assessing astrocytic Ca^{2+} signaling in the cortex of awake and naturally sleeping *Fmr1* mutant mice while monitoring brain rhythms and behavior. We hypothesize that astrocyte Ca^{2+} signaling signatures associated with sleep phases will be altered in the FXS mice.

Disclosures: A. Anding: None. **P. Ragunathan:** None. **P. Zhong:** None. **A. Dunaevsky:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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Topic: A.07. Developmental Disorders

Support: MUR PRIN 2022 grant n. 2022CFP7RF
Regione Lazio FSE 2014–2020 grant n. 19036AP000000019
Regione Lazio FSE 2014–2020 grant n. A0112E0073

Title: Rebalancing Neuronal Activity in 2D and 3D human iPSC based Fragile X disease models modulating the adenosine system

Authors: *C. D'ANTONI[1,2], F. CORDELLA[4], S. GHIRGA[2], C. SANCHINI[3], B. BASILICO[5], E. DEBBI[7,2], F. NISTRI[6], S. DI ANGELANTONIO[8];
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Abstract: Intellectual disabilities significantly impact the population, with Fragile X Syndrome (FXS) emerging as a prominent neurodevelopmental disorder and a leading heritable cause of Autism Spectrum Disorders (ASDs). FXS arises from the absence of the fragile X mental retardation protein (FMRP), a crucial regulator of mRNA associated with synaptic plasticity and neuronal growth. Despite valuable insights gleaned from animal models, disparities across species have impeded the translation of these findings into efficacious human therapies. The advent of human induced pluripotent stem cells (hiPSCs) has revolutionized this domain by providing a model for FXS incorporating cells from patients harboring the mutation.
In this work we deeply analized neurodevelopmental alterations in FXS at both cellular and network levels utilizing hiPSC-derived 2D and 3D cultures from FXS patients and healthy controls. These models serve as robust instruments for delineating FXS pathologies and propelling drug discovery. Our characterization of a 2D culture system comprising neural progenitors, neurons, and glial cells unveiled a persistent neural progenitor population,

elucidating FMRP's role in progenitor cell proliferation and cortical specialization.
Further investigation into glutamatergic and GABAergic synaptic development, coupled with calcium activity recordings within neuronal networks, pointed to excessive activity and developmental delays, consonant with recognized FXS attributes. Additionally, we employed NanoString nCounter analysis using the Neuropathology Panel to analyze gene expression profiles, highlighting a rescue of several differentially expressed genes observed in both patient-derived and knockout (KO) iPSC models.
Leveraging this robust cellular platform, we probed the therapeutic efficacy of istradefylline, an A2A receptor antagonist previously evaluated in FMRP-KO mice. Chronic administration of this antagonist markedly mitigated abnormalities in cortical development and network activity in FXS cultures. This investigation not only corroborates the therapeutic promise of istradefylline for FXS but also underscores the pivotal role of humanized models and advanced genetic analysis in advancing treatments for neurodevelopmental disorders.

Disclosures: C. D'Antoni: None. **F. Cordella:** None. **S. Ghirga:** None. **C. Sanchini:** None. **B. Basilico:** None. **E. Debbi:** None. **F. Nistri:** None. **S. Di angelantonio:** F. Consulting Fees (e.g., advisory boards); D-Tails s.r.l..

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR319.06/A49

Topic: A.07. Developmental Disorders

Support: NIH Grant R15S088776.

Title: Consequences of Chronic Early Life Stress in the Behavioral Manifestation of Fmr1 Knockout Mice

Authors: *K. J. BLANDIN[1], T. R. BRADISH[1], D. A. NARVAIZ[2], J. J. THAYIL[1], C. V. LAU[1], J. N. LUGO, Jr.[3], C. S. ENYERIBE[4];
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Abstract: Rationale: Fragile X syndrome (FXS) is the most prevalent inherited cause of intellectual disability and is marked by a mutation in the FMR1 gene, diminishing translation of the Fragile X metabotropic ribonucleoprotein (FMRP). The consequent deficiency in FMRP leads to disruptions in synaptic plasticity, neuronal connectivity, and neurotransmitter regulation, essential brain development. These disruptions underlie many of the observable behavioral deficits associated with the syndrome. Research suggests that chronic stress prenatally and during adulthood exacerbates cognitive and behavioral deficits observed in Fmr1 knockout (KO) mice, such as impairments in learning and memory, anxiety-like behaviors, and altered social

interactions. The long-term effects of chronic early life stress within the murine model remain undefined. Studying the interplay of genetic vulnerability and environmental stress, like chronic stress in Fmr1 KO mice, offers key insights into FXS mechanisms, guiding the development of innovative treatments. Methods: Male C57 wildtype and Fmr1 KO pups were used to simulate the most severe phenotype within the genetic mutation. Chronic early life stress was induced using a limited bedding paradigm postnatal day (PD) 2 through 9, using wire mesh over the typical amount of bedding and access to two-thirds of the standard nestlet for nesting. At PD 9 all mice are returned to standard rearing conditions until weaning at PD21. At PD 10, pups undergo isolation-induced ultrasonic vocalizations and are clipped for genotype, with an n=12 per group. At four months of age, stress-exposed and controlled undergo behavioral testing to assess locomotor activity, anxiety-like behavior, social, repetitive behavior, learning and memory, and sensorimotor gating. Results: Preliminary results reveal that chronic stress significantly decreases short-term body weight in both genotypes ($P<.001$) at PD10 before USV recording. Within only stress-exposed adult behavior data currently collected with n=6 per genotype, there is no significant difference in locomotor activity, repetitive/restrictive behavior, or anxiety-like behavior. Conclusions: Limited bedding regardless of genotype decreases body weight acutely following chronic stress. Currently, adult behavior suggests no effect of genotype within those exposed to chronic stress.

Disclosures: K.J. Blandin: None. **T.R. Bradish:** None. **D.A. Narvaiz:** None. **J.J. Thayil:** None. **C.V. Lau:** None. **J.N. Lugo:** None. **C.S. Enyeribe:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

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Program #/Poster #: PSTR319.07/A50

Topic: A.07. Developmental Disorders

Support: R01 MH084989
Barry Goldwater Foundation Scholarship
Vanderbilt Undergraduate Summer Research Program LittleJohn Scholarship

Title: Linking Fragile X Syndrome (FXS) and Glycogen Storage Disease (GSD)

Authors: *A. GURIJALA, E. RUSHTON, K. S. BROADIE;
Biol. Sci., Vanderbilt Univ., Nashville, TN

Abstract: A classic patient case double mutation of Fragile X Mental Retardation Protein (FMRP; FXS) and Phosphorylase Kinase Regulatory Subunit Alpha 2 (PHKA2; GSD) has symptoms far more severe than either disease alone. We hypothesized a FMRP-PHKA2 interaction based on unsustainably elevated metabolic demand, and tested this hypothesis with Drosophila disease models. FXS and GSD both manifest neurodevelopmental defects impairing

coordinated movement. In Drosophila larvae, we find double heterozygous mutants show significantly altered motor behavior compared to single heterozygotes. After starvation, coordinated movement is slowed across all genotypes, with no significant differences remaining. We next assayed muscle and neuromuscular junction (NMJ) defects. FXS and GSD disease models, as well as the double heterozygous mutants, all show significant defects in NMJ mitochondrial distribution. After starvation, control animals show a significant loss of NMJ MitoTracker fluorescence (measuring mitochondrial function), whereas GSD animals exhibit no effect and are comparable to the starved controls. FXS and GSD disease models, as well as the double heterozygous mutants, all show muscle regions lacking functional mitochondria surrounding the NMJs. We will soon be testing NMJ function using two-electrode voltage-clamp electrophysiology in single and double mutants, and expect to report these findings at the SfN meeting. We next assayed the underlying metabolic function. Fat quantification assays show FXS model larvae possess lower fat reserves compared to GSD model and control animals. After starvation, there is greater fat retention in FXS/GSD double heterozygous mutants. Fat Body Protein 1 (FBP-1) controls fat storage vs. utilization. GSD model larvae have significantly higher FBP-1 levels compared to FXS model and control animals. Interestingly, FXS model adults have extremely high FBP-1 levels, suggesting aberrant metabolic function. We are currently testing the balance of fat and glycogen storage. One potential mechanism is the elevated Glycogen Synthase Kinase-3 (GSK3) levels characterizing the FXS disease state. GSK3 knockdown reduces PHKA2 mRNA levels, whereas GSK3 overexpression elevates the mRNA levels. These results suggest the FXS disease state with heightened GSK3 typically requires elevated PHKA2 to breakdown glycogen, which is why stronger phenotypes occur when paired with GSD caused by lowered PHKA2 levels. We are testing PHKA2 enzymatic activity with phosphorylase and ATP assays to test metabolic efficacy in single and double mutants. This work is supported by R01 MH084989 to K.B. and a Barry Goldwater Scholarship to A.G.

Disclosures: A. Gurijala: None. **E. Rushton:** None. **K.S. Broadie:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR319.08/A51

Topic: A.07. Developmental Disorders

Title: Investigating Electroretinography Biomarkers for Altered Visual Processing in Fragile X Syndrome

Authors: *Q. PU[1], T. SEKHAR[1], M. T. STANLEY[1], E. BERRY-KRAVIS[2];
[1]Rush Med. Col., Chicago, IL; [2]RUSH Pediatric Neurosciences F.A.S.T. Ctr. for Translational Res., Rush Univ. Med. Ctr., Chicago, IL

Abstract: Background:
Fragile X syndrome, a neurodevelopmental disorder, is associated with altered neural processing

of visual information and sensory abnormalities that correlate with behavioral impairments. Identifying ERG biomarkers can provide valuable insights into the neurophysiological mechanisms underlying these symptoms and help with identifying treatment effects.

Methods:

Electroretinography (ERG) readings were collected from individuals with fragile X syndrome (FXS) under light-adapted conditions using a handheld RETeval® ERG device. The ERG protocol included a single flash at 85 Td.s white at 2 Hz and a repeated train of flashes (flicker) at 85 Td.s white at 28.3 Hz against a background of 850 Td. For the single flash, we analyzed the amplitude of the β-wave, and for the flicker, we measured the flicker amplitude. Data collection was conducted for both eyes, OD (right eye) and OS (left eye), resulting in 26 datasets across 20 unique individuals. Healthy controls will be recruited for subsequent comparison of the obtained results.

Results:

Of the data collected, around 46% of OD measurements (11 out of 24) and 60% of OS measurements (13 out of 22) were below the 5^{th} percentile of the normal range. For the flash β-wave amplitude, around 29% of OD measurements (4 out of 14) and 57% of OS measurements (8 out of 14) were below the 5^{th} percentile of the normal range. For the flicker amplitude, around 78% of OD measurements (7 out of 9) and 75% of OS measurements (6 out of 8) were below the 5^{th} percentile of the normal range. Some tests yielded inconclusive or null results, resulting in varying totals for OD and OS measurements.

Conclusion:

These results indicate a considerable percentage of abnormal β-wave and flicker amplitude measurements in individuals with fragile X syndrome, consistent with altered visual processing and sensory abnormalities. The presence of inconclusive or null results further underscores the challenges in conducting electroretinography (ERG) with FXS patients, who often have difficulty remaining still during testing, especially during flicker assessments. Future studies should include healthy controls for comparison and consider the challenges of testing in this population to better identify potential ERG biomarkers for fragile X syndrome.

Disclosures: Q. Pu: None. **T. Sekhar:** None. **M.T. Stanley:** None. **E. Berry-Kravis:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR319.09/A52

Topic: A.07. Developmental Disorders

Title: Effects of FMRP re-expression throughout development on EEG and behavioral phenotypes in a mouse model of fragile x syndrome

Authors: *C. SCARAMELLA[1], K. A. RAZAK[2];
[1]Univ. of California, Riverside, Riverside, CA; [2]Psychology, Univ. California, Riverside, Riverside, CA

Abstract: Fragile X Syndrome (FXS) is a leading known genetic cause of intellectual disability, and symptoms including anxiety, social deficits, sensory sensitivity, processing deficits and language delays, overlap considerably with autism spectrum disorders. FXS is the result of transcriptional silencing of the *Fmr1* gene, which leads to a lack of fragile X messenger ribonucleoprotein (FMRP). *Fmr1* knock-out (KO) mouse models of this disorders show consistently similar phenotypes to those seen in humans with FXS. In particular, electroencephalogram (EEG) studies have identified atypical neural oscillations that are remarkably similar in FXS individuals and mouse models, implicating cortical circuit dysfunction and highlighting the clinical significance of EEG phenotypes to identify relevant biomarkers. Specifically, EEG studies from our lab have consistently shown increased excitability but reduced habituation to repeated sound exposure as well as impaired synchrony to time varying stimuli in *Fmr1* KO mice Additionally, work in our lab has identified robust behavioral phenotypes in *Fmr1* KO mice such as deficits in reversal learning, decreased nest building and increased locomotor activity when presented with loud auditory stimuli compared to wild-type controls. However, it remains unclear how FMRP levels contribute to these phenotypes throughout development. It is also unclear whether FMRP re-expression in the adult brain is sufficient to reverse cortical deficits or if interventions early in development are necessary to prevent lifelong pathology. Thus, using epidural screw electrodes in the auditory (AC) and frontal cortices (FC), we recorded auditory event related potentials (ERPs), auditory steady state response (ASSR), and auditory temporal processing with gap-in-noise ASSR stimulus in adolescent (p35) and adult male (p80-p90), freely moving c57bl6/j mice, after undergoing treatment with tamoxifen to re-express FMRP 15 days prior. We also examined the effects of FMRP re-expression at both developmental timepoints on behaviorally relevant phenotypes including nest building, hyperactivity, and cognitive flexibility. The results of these studies will have major implications in identifying treatment windows, as well as the potential utility of gene therapy past early development in humans with FXS and related spectrum disorders.

Disclosures: C. Scaramella: None. **K.A. Razak:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

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NIH P50 HD10353
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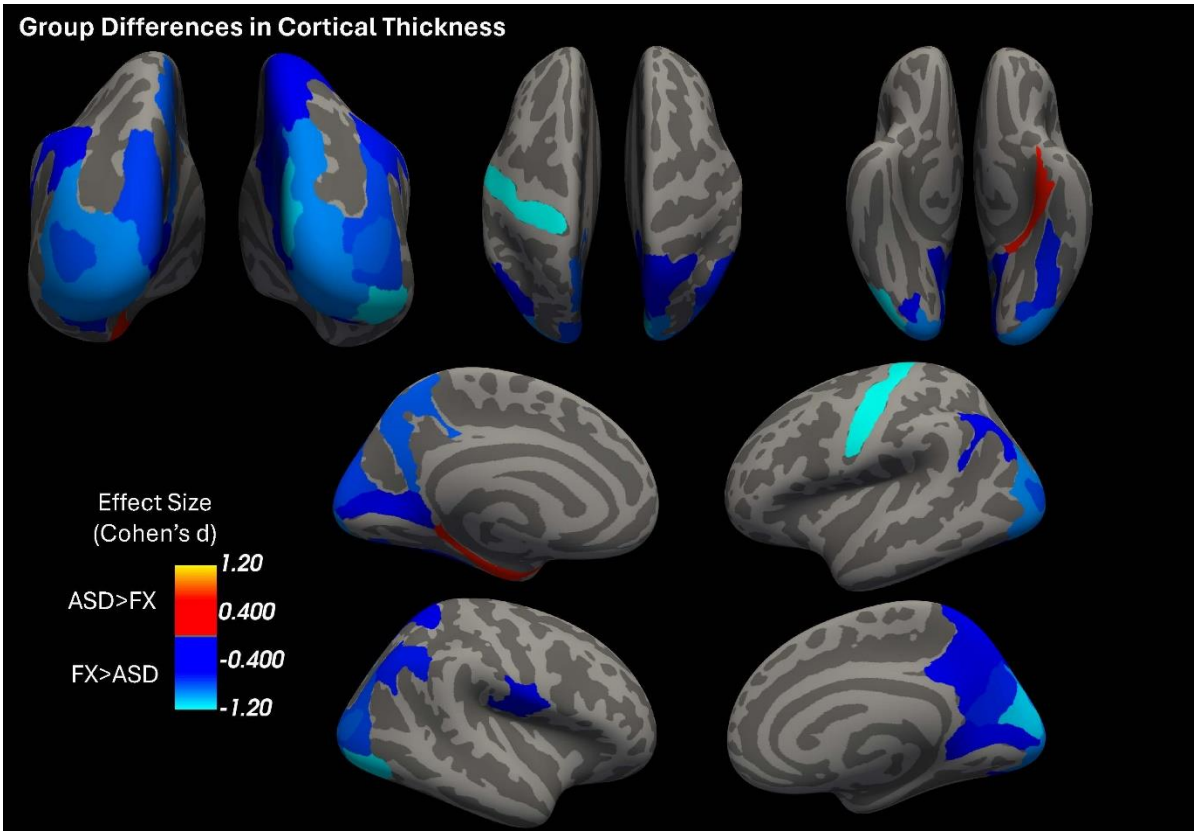
Hartwell Foundation's Individual Biomedical Award
Austin Faculty Fellowship

NIH R01 HD094715
NIH U54 HD090256

Title: Cerebral Cortex Morphometry and Relaxometry in Male Children with Fragile X Syndrome and Autism

Authors: *J. M. GUERRERO-GONZALEZ[1], A. LOWE[2], S. KECSKEMETI[2], B. TRAVERS[3], A. ALEXANDER[2], A. STERLING[4];
[1]Med. Physics, Waisman Ctr., Univ. of Wisconsin - Madison, Madison, WI; [2]Waisman Ctr., Univ. of Wisconsin - Madison, Madison, WI; [3]Waisman Ctr., Univ. of Wisconsin-Madison, Madison, WI; [4]Communication Sci. and Disorders, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Introduction: Sources estimate 30-60% of males with Fragile X Syndrome (FXS) meet diagnostic criteria for autism spectrum disorder (ASD)[1,2,3]. Therefore, characterizing shared neuroanatomical characteristics and differences between FXS and ASD is crucial to better understand the phenotypic overlap between these disorders and to potentially inform therapeutics. Yet, few neuroimaging studies have analyzed FXS and ASD in tandem. This analysis uses cutting-edge quantitative MRI to investigate brain cortex thickness and myelination in male children with FXS and ASD.
Methods: Cortical thickness and R1 (longitudinal relaxation rate, sensitive to myelination)[4] were extracted from 74 cortical regions per hemisphere of the Destrieux[5-7] atlas in 47 participants (11 FXS, 36 ASD), ages 9-18 years. Brain imaging used MPnRAGE[4], which enables high-resolution, motion-corrected whole brain R1 maps and structural images. Each measure was linearly modeled with age, group, and age-by-group terms.
Result: s Compared to ASD, cortical thickness in occipital and parietal regions was significantly higher ($p < 0.05$, FDR corrected) in FXS. In the medial para-hippocampal gyrus, cortical thickness was significantly higher ($p < 0.05$, FDR corrected) in ASD. In all these regions, a negative relationship of cortical thickness with age was observed in both groups. No significant group differences in R1 were found after multiple comparisons corrections.
Discussion: Main findings from this study indicate increased cortical thickness in FXS compared to ASD, primarily in low level visual and auditory processing areas of the occipital, parietal, and temporal lobes. Both ASD and FXS individuals have visual and auditory differences compared to neurotypical individuals. However, the increased cortical thickness in the FXS group may be an indication that early sensory processes in FXS and ASD are different, even if mechanisms associated with higher level cognitive processes are similar. Analyses of these findings in relation to diagnostic and behavioral measures of speech and communication are ongoing.



Disclosures: J.M. Guerrero-Gonzalez: None. **A. Lowe:** None. **S. Kecskemeti:** None. **B. Travers:** None. **A. Alexander:** None. **A. Sterling:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

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Program #/Poster #: PSTR319.11/A54

Topic: A.07. Developmental Disorders

Support: Project # GRT-2022A-2142 Fondation Lejeune Paris

Title: Impaired response to cellular stress and senescence in a mouse model of Fragile X syndrome

Authors: *M. CATANIA, S. D'ANTONI, M. SPATUZZA;
Inst. for Biomed. Res. and Innovation, Natl. Res. Council (CNR), Catania, Italy

Abstract: Fragile X Syndrome (FXS) is a frequent form of inherited intellectual disability and a leading monogenic cause of autism, which is caused by lack/reduction of fragile X messenger ribonucleoprotein1 (FMRP), an RNA-binding protein involved in several aspects of RNA

metabolism. Abnormal expression of proteins at synapses underlies brain dysfunction in FXS. FMRP is also implicated in DNA damage response and is a component of stress granules (SGs), cytoplasmatic aggregates that form in response to stress and are protective against apoptosis. Evidence in the Fmr1 knockout mouse model of FXS suggests increased oxidative stress in the brain and increased susceptibility to apoptosis. However, how neurons and glial cells cope with chronic stress in the absence of FMRP and how this can affect the trajectory of disease with aging is presently unknown. Oxidative stress and DNA damage can also trigger cellular senescence. Therefore, we investigated both sensitivity to stress and senescence in FXS mice. We studied SGs formation and cell survival in wild-type (WT) and *Fmr1* knockout (KO) cultured neurons and astrocytes after exposure to oxidative stress by immunocytochemistry and MTT assay. We used senescence-associated-beta-galactosidase (SA-beta-gal) assay to reveal the senescent phenotype in WT and *Fmr1* KO brain slices. We detected: 1. a lower number of SGs in *Fmr1* KO astrocytes and 2. a lower cell survival in *Fmr1* KO neurons and astrocytes compared to WT astrocytes upon exposure to oxidative stress; 3. an increased SA-b-gal staining in *Fmr*1 KO brains compared to WT counterparts. These results suggest that lack of FMRP sensitizes to oxidative stress-induced damage and accelerates senescence, possibly contributing to brain dysfunction in FXS.

Disclosures: M. Catania: None. **S. D'Antoni:** None. **M. Spatuzza:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR319.12/A55

Topic: A.07. Developmental Disorders

Title: Neurolinguistic and plasma biomarkers in Fragile X Syndrome and Fragile X Premutation Carriers.

Authors: *J. KEALY[1], F. TRAINI[2], E. GRILLI[1], J. PINTO[1], S. WANINGER[1], M. BIANCHI[1]; [1]Ulysses Neurosci. Ltd., Dublin, Ireland; [2]Trinity Col. Dublin, Dublin, Ireland

Abstract: Fragile X Syndrome (FXS) patients and Fragile X Premutation Carriers (FXPCs) have an expansion of the trinucleotide repeat CGG in the FMR1 gene (Fragile X Messenger Ribonucleoprotein 1). A full mutation (>200 CGG nucleotide repeat expansion) leads to the neurodevelopmental disorder FXS, while a premutation (55-200 CGG repeat expansion) can lead to various conditions, including the disorder Fragile X Tremor-Ataxia Syndrome (FXTAS). FXTAS is considered a Parkinson Disease (PD)-like disorder that presents as a range of tremor and ataxia symptoms. In populations at risk of neurodegeneration, impaired or delayed retrieval of words from the mental lexicon is a potential marker of cognitive decline. Language dysfluencies have been observed in FXPCs, potentially indicating disruption in the lexical retrieval process. Here, three linguistic tasks were paired with plasma-based molecular analysis to compare between FXPCS and healthy controls.

Three linguistic tasks were administered to FXPCs (N=70) and healthy controls (N=52) to measure the following: 1. Language production through a picture naming task (objects vs actions), 2. Receptive language using a visual word paradigm task (objects vs actions) 3. Expressive language through a picture description task. Infrared Western Blot analysis was used for the analysis of alpha-tubulin post-translational modifications (PTMs) as markers of microtubule dynamics such as acetylated alpha-tubulin (Acet-Tub) and Tyrosinated/Detyrosinated alpha-tubulin (Tyr/Glu-Tubulin), while Neurofilament light (NfL) expression was measured using electrochemiluminescence. These markers were analysed in the plasma of patients with FXS (n = 24) and matched controls (n = 23); and in FXPCs (n = 14) and matched controls (n = 15).
The reaction time in FXPCS was significantly slower than healthy controls in the picture naming task for both objects and actions ($p<0.01$). Similarly, significantly slower reaction time was observed for both objects and actions in the receptive language task ($p<0.05$). Tyr/Glu-Tubulin was significantly decreased in FXS patients indicating decrease microtubule dynamics. NfL showed no differences between either patient group and healthy controls.
Our linguistic data on FXPCs contrasts with PD patients, who are more affected in retrieving action words, potentially because of the possible involvement of the basal ganglia network in action words production. The proposed approach may represent a important step for developing a tool for differential diagnosis of FXTAS and PD at its early stages, and for the development of appropriate biomarkers for drug discovery efforts in FXTAS.

Disclosures: J. Kealy: None. **F. Traini:** None. **E. Grilli:** None. **J. Pinto:** None. **S. Waninger:** None. **M. Bianchi:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR319.13/A56

Topic: A.07. Developmental Disorders

Title: Fmr1 deficiency enhances instrumental learning for social, but not food, rewards in both male and female FVB mice

Authors: M. LUONGO, S. BOUKOBZA, T. ZIMMER, S. SKLAR, C. EZE, E. TINCHER, A. FOOTE, A. LUHNOW, M. BEAUDRY, *B. ZUPAN;
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Abstract: Dysregulated social interaction is a core dimension of developmental disorders, including Fragile X Syndrome (FXS). The mouse model of FXS on the FVB background displays hypersociability and this phenotype can be induced by both *Fmr1* deficiency in the subjects and by maternal *Fmr1* deficiency. Using single and three-chamber sociability tasks, we found that both *Fmr1* and maternal *Fmr1*-deficient male mice display increased interaction time with a novel conspecific. This was associated with altered cfos activation in brain regions

relevant to social motivation and reward including the ventral tegmental area and nucleus accumbens shell. We were unable to assess female subjects for (hyper)sociability due to ceiling effects in these tasks. Here we aimed to measure motivation for and valuation of social reward across both sexes. We used an instrumental conditioning task on a progressive ratio (PR) schedule to obtain breakpoint values. Specifically, a 15-second indirect social interaction with a same-sex conspecific served as the social reinforcer while 33% sweetened condensed milk was used as the food reward. Following shaping and fixed ratio conditioning to reach learning criterion, mice underwent ten days of progressive ratio (PR3) trials. Subjects first completed social then, followed at least one week later by, food reward trials. Surprisingly, neither *Fmr1* genotype nor sex impacted breakpoint values, indicating that the valuation of and/or motivation for the social reinforcer did not differ between groups. A similar lack of difference in breakpoints was observed for the food reinforcer, although the condensed milk elicited higher breakpoints confirming it is a stronger positive reinforcer in this task. We also measured lever press rates and time to breakpoint during PR3 trials, neither of which differed across groups. However, a large difference emerged across *Fmr1* genotypes in both female and male mice in the proportion of subjects reaching criterion for the social reinforcer PR3 trials. Only one third of wild-type control mice met the learning criterion compared with 50-100% of *Fmr1* and maternal *Fmr1*-deficient subjects, while acquisition of the food-reinforced task ranged between 76-100% with no differences across groups. Additionally, all mice exhibited comparable social odor discrimination, indicating that differences in instrumental learning for a social reward are not likely caused by altered social cue detection and processing. In sum, our data suggest that both male and female *Fmr1* and maternal *Fmr1* deficient mice may exhibit an enhanced motivational drive for social interaction as measured by enhanced instrumental learning for social reward.

Disclosures: M. Luongo: None. **S. Boukobza:** None. **T. Zimmer:** None. **S. Sklar:** None. **C. Eze:** None. **E. Tincher:** None. **A. Foote:** None. **A. Luhnow:** None. **M. Beaudry:** None. **B. Zupan:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

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Program #/Poster #: PSTR319.14/A57

Topic: A.07. Developmental Disorders

Support: RSP21-40780-002

Title: Deep brain stimulation of medial septum corrects for abnormal behavior and, learning and memory deficit observed in FMR1-KO mice.

Authors: M. OUARDOUZ[1], A. E. HERNAN[3], M. MAHONEY[4], R. SCOTT[2];
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Abstract: Fragile X syndrome is a neurodevelopmental disorder caused by mutation in the Fragile X Messenger Ribonucleoprotein 1 (FMR1) gene. Dysregulation of FMR1 protein expression is the most common cause of intellectual disability in humans. Autism spectrum disorder features have been also reported in people with fragile X syndrome. Previous studies reported behavioral and cognitive abnormalities in FMR1-KO mice. The objective of this study was to use deep-brain stimulation (DBS) of the medial septum (MS) in FMR1-KO mice to ameliorate putative changes in behavior and long-term potentiation (LTP) in hippocampus. Wild-type mice and FMR1-KO mice were subjected to a battery of behavioral task. For DBS, a bipolar stimulating electrode was implanted in the MS. LTP experiments were carried in hippocampal slices. Excitatory post-synaptic field potential (fEPSP) was evoked by electrical stimulation and recorded in CA1 region. The initial slope of the fEPSP was used to access the change of excitatory synaptic transmission in response to high frequency electrical stimulation (HFS: 3 trains of 1 s at 100Hz at 20 s interval). FMR1-KO mice had impaired novel object place recognition task. DBS of the medial septum at 35 Hz but not at 7.5, 20 or 75 Hz was able to normalize the discrimination index in FMR1-KO. Stimulation of the medial septum at 35 Hz was also able to ameliorate social deficits as assessed by the discrimination index between object and male wild type mouse (Control: 0.263 $\pm$ 0.030, FMR1-KO: 0.168 $\pm$ 0.039 and FMR1-KO stim at 35 Hz: 0.394 $\pm$ 0.054). For the inhibition avoidance task the initial latency to enter the dark chamber was not different between the 3 groups (Control: 21.528 $\pm$ 3.604 s, FMR1-KO: 14.812 $\pm$ 3.801 s and FMR1-KO DBS at 35 Hz: 49.238 $\pm$ 3.801 s). After entering the dark chamber, the door was closed, and the animal receive an electrical shock. This procedure was repeated 3 times at 2 minutes interval. 24 hours after, the latency to enter the dark chamber was lower for FMR1-KO compared to control and restored by DBS at 35 Hz (Control: 550 $\pm$ 49.24 s, FMR1-KO: 215.80 $\pm$ 78.24 s and FMR1-KO stim at 35 Hz: 600 $\pm$ 0 s). We also find evidence of impaired LTP in FMR1-KO mice, which is restored by DBS at 35Hz. HFS induced an increase of the fEPSP slope in control mice by 97.01 $\pm$ 19.68 % but to lesser extent in FMR1-KO mice (36.13 $\pm$ 7.66 % 30). DBS of the medial septum at 35 Hz restores LTP expression (121.32 $\pm$ 19.10 %). Our results show that DBS of the medial septum improves cognitive deficits in FMR1-KO both at the behavioral and cellular level. DBS of the medial septum may be one of the avenues to correct for abnormal behavioral and learning and memory deficits observed in fragile X syndrome.

Disclosures: M. Ouardouz: None. **A.E. Hernan:** None. **M. Mahoney:** None. **R. Scott:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

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Program #/Poster #: PSTR319.15/A58

Topic: A.07. Developmental Disorders

Support: Project FONDECYT Regular 1210069
ANID Scholarship Program, DOCTORADO NACIONAL, 2020 –

21200657
UMD MPower Seed Grant Challenge

Title: Altered odor-mediated social behavior in a model of fragile X Syndrome

Authors: L. C. IRVINE[1], M. NAVARRETE[2], J. C. ZEGERS-DELGADO[1], *R. C. ARANEDA[3], J. MPODOZIS[2], A. F. NUNEZ-PARRA[2];
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Abstract: Fragile X Syndrome (FXS) is a neurodevelopmental disorder characterized by intellectual disability and difficulties in social interaction. In mice, the accessory olfactory bulb (AOB) is implied in the processing of chemical cues that trigger social and sexual behaviors. In addition, the olfactory bulb shows high levels of Fragile X Messenger Ribonucleoprotein (FMRP) during neurodevelopment, the absent protein in FXS.Here, we show that the Fmr1 KO mice, a model of FXS, exhibit abnormal odor-mediated social behaviors. Male Fmr1 KO mice show reduced investigation of conspecifics and social odors (urine and soiled bedding), as well as impaired discrimination between social odors. However, discrimination of non-social odors was not impaired neither was the overall motor activity. A neuroanatomical analysis showed that the glomerular layer volume in the anterior region of the AOB was smaller in Fmr1 KO compared to WT mice. Together, these findings suggest that disruption in AOB signaling can explain the lesser sociability of these mice. Accordingly, we found that mitral cells (MCs), projection neurons of the AOB, exhibit altered excitability in Fmr1 KO mice. The firing in MCs, elicited by current stimuli, was lower in Fmr1 KO mice. In conclusion, the anatomy and physiological differences in the AOB of the Fmr1 KO mouse could partly explain their deficit in odor-mediated social behavior.

Disclosures: L.C. Irvine: None. **M. Navarrete:** None. **J.C. Zegers-Delgado:** None. **R.C. Araneda:** None. **J. Mpodozis:** None. **A.F. Nunez-Parra:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR319.16/A59

Topic: A.07. Developmental Disorders

Support: NIH R01MH050047
the Kelvin Foundation
the Canel Family Fund

Title: Progressive alterations in neural activation and sensitization during face processing in fragile X syndrome: A longitudinal perspective

Authors: *Y. GAO[1], R. LI[3], Q. MA[4], K. L. BARTHOLOMAY[5], A. LIGHTBODY[6,1], A. L. REISS[2];
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Abstract: Fragile X syndrome (FXS) is a genetic condition associated with increased risk for social anxiety and avoidance behaviors. Employing functional near-infrared spectroscopy (fNIRS), our prior work unveiled aberrant neural responses to facial stimuli among young girls with FXS in a cross-sectional study. Upon this foundation, we investigated whether abnormalities in neural activation and sensitization exacerbate with age in a cohort of 65 girls with FXS, ages 6-16 years, relative to 52 age-matched controls matched for verbal abilities. Functional NIRS data were collected at two time points, 2.80.6 years apart, during a face-processing task. Linear mixed-effects models examined longitudinal neural profiles in girls with FXS and controls. Correlational analysis examined associations between neural sensitization (increasing neural response to repeated stimuli), and clinical symptoms. Among girls with FXS, 32 underwent one, and 24 received two fNIRS scans; and 21controls underwent one, and 29 received two scans. Brain activations in the right middle and superior frontal gyri were greater in FXS compared to controls at both time points. Neural sensitization also increased in FXS at a higher rate relative to controls within the superior frontal gyrus during responses to upright faces. Among the girls with FXS, sensitization in the superior frontal gyrus positively correlated with longitudinal increases in anxiety and social avoidance scores, examined by the Anxiety, Depression, and Mood Scale and Social Responsiveness Scale-2 Total Score. These findings indicate a progressive increase of abnormal neural activation and sensitization in girls with FXS over time responding to face stimuli. This aberrant neural sensitization is associated with longitudinal changes in anxiety and social skills in girls with FXS. Neural response to facial stimuli may therefore provide a unique biomarker or target for intervention in this population

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Poster

PSTR319: Neurodevelopmental Disorders II

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR319.17/A60

Topic: A.07. Developmental Disorders

Support: P20GM113109

Title: Comparing cognitive and motor behavior of heterozygous FMR1 knockout across their lifespan

Authors: *B. SIVAYOKAN[1], E. ALFS-VOTIPKA[2], D. TURNER[2], D. CARAGEA[2], B. PLAKKE[3];
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Abstract: Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability, and a leading heritable single-gene cause of autism spectrum disorder. Expansions in the FMR1 gene cause loss of fragile X mental retardation protein (FMRP). The absence of this protein results in hyperconnectivity and hyperexcitability, leading to multiple consequences such as memory impairment and motor deficits. In humans, premutation carriers have less extensive expansions in the FMR1 gene, and develop a condition known as fragile X associated ataxia as they age. Animals with the heterozygous FMR1 gene, analogous to the human premutation carriers, also develop cognitive decline and ataxia in late adulthood. When do the deficits in heterozygous animals occur? This study used homozygous and heterozygous FMR1 knockout (KO) and wildtype animals and examined cognitive and motor behaviors across the lifespan. Wildtype, homozygous, and heterozygous KO Long-Evans rats (at least 12 per group) underwent a novel object recognition test between postnatal day (P) 60 and 70. This test was carried out over a span of three days. On the first day, the animals were allowed to explore five objects kept in the arena. On the second day, two of the objects were switched places, and on the final day, one object was replaced with a novel object. In addition, the animals underwent a rotarod test at P80 and a grip strength test for 4 days, at the age of 6 months. All tests were carried out by blind-to-condition researchers. Multilevel models were used to analyze all data. Results showed that all animals spent more time with the novel object ($p < .001$), irrespective of genotype or sex. There were no differences between groups on the maximum latency to fall in the rotarod test. However, homozygous KO animals tended towards greater improvement in latency in trial 2 over trial 1 ($p = .080$), suggesting possible acquisition of repetitive motor behavior. Grip strength increased over the course of 4 days for all animals ($p < .001$). Males had higher grip strength than females, irrespective of genotype ($p < .001$). Relative strength (grip strength divided by body weight) did not vary by sex, but varied according to the genotype, with the wildtype animals having lower relative strength than homozygous or heterozygous knockout animals ($p = .032$). These findings suggest that heterozygous FMR1 knockouts do not show memory impairment and motor deficits early in their lifespan.

Disclosures: B. Sivayokan: None. **E. Alfs-Votipka:** None. **D. Turner:** None. **D. Caragea:** None. **B. Plakke:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

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Program #/Poster #: PSTR319.18/A61

Topic: A.07. Developmental Disorders

Support: P20GM113109
USRG to B.P. From K State Univ
MPH Program Support Vet Med K State

Title: Maternal choline supplementation is protective against maternal immune activation in the prefrontal cortex of adolescent rats

Authors: C. KING, *B. PLAKKE;
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Abstract: Choline supplementation during pregnancy and lactation provides protection from neurodevelopmental disorders. One unique property of choline is its ability to instigate anti-inflammatory signaling through the alpha-7 nicotinic acetylcholine receptor (α7nAChR). The α7nAChR initiates PI3K/Akt cell survival signaling for antioxidant defenses and JAK2/STAT3 signaling to counteract inflammatory NF-κB signaling. This study tested whether maternal choline supplementation could mitigate the effects of maternal immune activation (MIA), which is a risk factor for autism and schizophrenia. To induce MIA in pregnant rats, dams were given a single intraperitoneal injection of high molecular weight poly(I:C) on gestational day 15, which corresponds to the second trimester of human pregnancy (n=5 saline dams, n=13 poly(I:C) dams). Six of the poly(I:C) dams also received dietary choline chloride supplementation (5g/kg) throughout pregnancy and lactation. Offspring were tested behaviorally early and middle adolescence (postnatal days (P) 28 and 50, respectively, n=152). After behavioral testing, animals were euthanized by decapitation under deep anesthesia, and their prefrontal cortices (PFCs) were collected. PFCs were used for Milliplex cytokine and cell si gnaling assays (n=84; P28 n=42, P50 n=42) Results were analyzed non-parametrically with Kruskal-Wallis tests followed by Dunn's test post hoc. No sex effects were observed for any assay, so all results are reported regardless of sex. At P28, MIA offspring had significant reductions in the expression of IL-4, an anti-inflammatory cytokine, compared to controls (p=0.036). This was rescued by maternal choline supplementation (p<0.001) to levels indistinguishable from controls. At P50, maternal choline-supplemented MIA offspring had greatly increased IL-4 levels relative to both controls (p<0.001) and MIA-only animals (p-0.032). At both P28 and P50, MIA offspring had reduced protein kinase B/Akt expression and activation (P28 p<0.039; P50 p=0.018), which was completely rescued by maternal choline supplementation at both ages (P28 p<0.001, P50 p=0.010). Maternal choline supplementation also blunted age-related increases in IL-6 in the MIA group and facilitated an age-related increase in the anti-inflammatory cytokine IL-10. IL-4 is a key factor in polarizing microglia to the homeostatic M2 state, a switch that is also underpinned by choline metabolism. The increased expression of IL-10, which is released from M2 microglia, supports this. Together, these findings suggest that maternal choline supplementation may be an effective intervention to blunt the impacts of MIA on the developing fetus.

Disclosures: C. King: None. **B. Plakke:** None.

Poster

PSTR319: Neurodevelopmental Disorders II

Location: MCP Hall A

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Topic: A.07. Developmental Disorders

Support: Women's Brain Initiative Pilot Award
2023 NARSAD Young Investigator Grant

Title: Sleep macro and micro-architecture predicts altered neurodevelopment in boys and girls with neurodevelopmental disorders

Authors: *N. KOZHEMIAKO[1,2], S. PURCELL[1,2];
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Abstract: Background: Many studies have utilized the framework of predicting chronological age using neuroimaging data, assuming that discrepancies from observed age serve as a putative indicator of overall brain health. In this study, we utilized sleep polysomnography to establish a unified model for predicting chronological age and investigated: 1) the transferability of the model across different cohorts, 2) whether variances between predicted and chronological age distinguished children with neurodevelopmental disorders (NDD) from typically developing children, and 3) the effect of sex on age prediction.**Methods:** The primary discovery dataset comprised 2,800 individuals (2.5-17.5 years) with whole-night PSGs from NCH Sleep Databank (from the National Sleep Research Resource). We defined six subsets within the NCH sample based on the presence of the following diagnoses: autism spectrum disorder, attention deficit and hyperactivity disorder, intellectual disabilities (ID), Down syndrome (DS), cerebral palsy, and epilepsy. Sleep EEG was processed using an open-source toolbox Luna (zzz.bwh.harvard.edu/luna). We used 70% of the NCH sample as a training set and 30% as a testing set (individuals with NDD were excluded from both sets). To test the model's transferability, we employed two additional datasets, the Childhood Adenotonsillectomy Trial (CHAT, N=1,213), and the Pediatric Adenotonsillectomy Trial for Snoring, (PATS, N=627).**Results:** The model trained to predict an individual's chronological age performed with high accuracy (r=0.93 in the held-out NCH testing sample and r=0.85 in a second independent replication sample (PATS). Our finding indicated that EEG-based age predictions reflected clinically meaningful neurodevelopmental differences. For example, compared to typically developing children, those with NDD showed greater variability in predicted age, and children with DS or ID had significantly younger brain age predictions (respectively, 2.1 years, $p=9\times10^{-9}$ and 0.8 years, p=0.02 less than their chronological age) compared to age-matched non-NDD children. Our findings also indicated generally no significant effect of sex on age prediction in the testing samples as well as in the NDD groups. One exemption was a trend in the ADHD boys to have less accurate prediction in absolute terms compared to girls (p-value=0.06).**Conclusion:** Overall, our results indicate that sleep architecture offers a sensitive window for characterizing brain maturation, suggesting the potential for scalable, objective sleep-based biomarkers to measure typical and atypical neurodevelopment.

Disclosures: N. Kozhemiako: None. **S. Purcell:** None.

Poster

PSTR320: Motor Systems

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR320.01/A63

Topic: A.08. Development of Neural Systems

Support: NSF-SCH 2123972
NSF-SCH 2124405

Title: The Effect of Movement on Cardiorespiratory Function in Preterm Infants

Authors: *L. BLODGETT[1,2], A. RICHARDSON[5], I. KALHORO[6], C. MIHOVA[6], D. REID[8], J. CHANG[6], A. GROVES[7], D. PAYDARFAR[6], D. STERNAD[3,2,4];
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Abstract: Nearly 10% of all infants in the United States are born preterm, defined as <37 weeks' gestational age (GA). Preterm infants are at increased risk for developing neuromotor disorders, including cerebral palsy, autistic spectrum disorder, and attention deficit disorder (Fitzgerald et al., 2018). In addition, preterms often face life-threatening cardiorespiratory events, including apnea, bradycardia, and hypoxia (Poets et al., 1993). This research aims to investigate the features of cardiorespiratory immaturity and the causal relationship between motor activity and cardiorespiratory function in premature infants.12 subjects ranging from 24 to 32 weeks GA were analyzed longitudinally over 4 to 8 weeks. Subjects resided in Ascension Seton's Neonatal Intensive Care Unit (NICU) in Austin, TX. The obtained data were restricted to routine care signals, including ECG, oxygen saturation (Sp02), photoplethysmography (PPG), and respiratory rate. The non-invasive nature of our study enabled us to collect data from subjects over their entire stay in the NICU. Movements were identified via a wavelet-based algorithm that extracted the time intervals of motion artifacts in the PPG signal. Heart rate was extracted from RR intervals in the ECG signal. The analyses focused on movement patterns and cardiac response to motor activity. Average heart rate across preterm infants was measured as a function of movement duration and age. The frequency of movement was also assessed relative to bradycardic and hypoxic episodes. Finally, information about neurodevelopmental disorders was used to determine whether outliers in the data correspond to individuals with neuromotor impairments. It also served to distinguish healthy versus abnormal patterns of movement maturation. Movements were found to occur most frequently before and during bradycardic and hypoxic episodes. The termination of a cardiorespiratory event was followed by a decrease in movement frequency. In healthy infants, increases in movement duration were closely mirrored by an increase in heart rate. However, for infants categorized as extremely preterm (<28 weeks GA), the heart rate after movement appears stunted and less responsive. This suggests that as the healthy preterm matures, it develops a more robust cardiac response to movement. Finally, infants with neuromotor disorders displayed abnormal movement maturation patterns. These results present first steps towards prevention of adverse cardiorespiratory events and better

understanding of the delicate interplay between movement and cardiorespiratory function. Our research aims to increase survival rates and improve outcomes of preterm infants.

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Poster

PSTR320: Motor Systems

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR320.02/A64

Topic: A.08. Development of Neural Systems

Support: NIH R35 NS122266
NIH T32 HD007414

Title: Adaptive learning in an unconstrained bimanual context across developing children aged 8-17 years

Authors: *R. VARGHESE[1,2], C. ROSSI[3], H. TRIPP[4], L. MALONE[4], A. J. BASTIAN[3,2];
[1]Johns Hopkins Med. Institutions, Baltimore, MD; [2]Kennedy Krieger Institute, Baltimore, MD; [3]Neurosci., Johns Hopkins Univ., Baltimore, MD; [4]Kennedy Krieger Inst., Baltimore, MD

Abstract: Nearly all human motor learning occurs in unconstrained naturalistic environments where the learner can benefit from multiple sources of feedback and can explore a wide range of movement patterns. Over the course of development and throughout adulthood, the nervous system can acquire internal models of movement and adapt them in response to errors. The purpose of this study was to understand how children aged 8 to 17 years (n=95) adapt new bimanual coordination patterns compared to adults (n=21). We utilized a realistic 3D visuomotor gain adaptation task presented through a virtual reality headset with full visual feedback of the arm and hand to create an unconstrained, naturalistic environment. Participants were asked to "feed birds" by lifting a virtual plate of grapes using virtual representations of their own hands. They received binary audiovisual feedback when the plate reached the target zone. The visuomotor gain perturbation was applied gradually to the right hand, such that the virtual right hand appeared to move less than the true hand. This perturbation was removed abruptly during a washout block. We found an age-dependent performance effect in both baseline and adaptation such that older children and adults made faster, more accurate, and more successful movements compared to younger children. To capture learning strategies, we measured interlimb coordination as the covariance in speed rescaling between the two hands early in the movement. We then used the associated eigenvalues (λ) to represent exploration of coordination patterns. During adaptation, 8–9 year-olds explored a wider range of interlimb coordination patterns compared to adults ($\lambda_{8\text{-}9}$ = [1.06, 0.04] vs λ_{adults} = [0.21, 0.01], $p<0.001$). The exploration of interlimb coordination approached adult levels by 12-13 years of age ($\lambda_{12\text{-}13}$ = [0.42, 0.02]).

Aftereffects in interlimb coordination patterns, a hallmark of adaptive learning, were significant in early washout and followed the same age-dependent trend. These data suggest that the capacity and strategy for learning new bimanual coordination patterns follows a developmental trajectory that is not adult-like until adolescence. Results from this research are relevant for understanding motor learning in childhood under unconstrained, naturalistic conditions.

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Poster

PSTR320: Motor Systems

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Program #/Poster #: PSTR320.03/A65

Topic: A.08. Development of Neural Systems

Title: Potential Influences of Perinatal Exposure to Anti-Aging Supplements

Authors: *H. M. RUBY[1], V. R. RIESGO[2], J. WILLING[2];
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Abstract: Research into the use of dietary supplements to reduce symptoms of cognitive decline in aged populations is increasing. Currently, two supplements gaining prominence are nicotinamide mononucleotide (NMN) and resveratrol. Previous studies utilizing animal models reported that both NMN and resveratrol slow cognitive decline by reducing apoptotic cell death. Additionally, these supplements are marketed as beneficial for overall brain health, which creates a diverse consumer population, including pregnant mothers. In fact, these have even been recommended for pregnant women to promote a healthy pregnancy, given their anti-inflammatory properties. The possible consumption of NMN and resveratrol by pregnant mothers raises concern as both supplements may cross the placenta and interact with the developing fetus. Given one of their mechanisms in aged subjects, perinatal exposure to these substances could also disrupt levels of apoptosis during early development, which is critical for organizing neural circuits. In the present study, we divided Long Evans dams into four exposure groups: NMN-exposed animals, resveratrol-exposed animals, animals exposed to both supplements, and control animals. Dosing for all groups at embryonic day 0 and continued until postnatal day (P)10. Offspring underwent neonatal behavioral testing on P5, P7, and P10. Tests included observations of rooting, righting, cliff-aversive, and crawling behaviors to assess sensory motor development. On P12, neonatal male and female brain tissue was collected. In littermates, adult behavioral testing occurred on P80 to observe possible long-lasting effects on hippocampal and PFC regulated behaviors. We also examined the effects of these supplements on reproductive success, body weight and total brain weight. Results suggest that perinatal exposure to these “anti-aging supplements” does alter neurodevelopment, neonatal behavior and adult behavior. This research may have implications not only for recommendations for pregnant women, but also for the study of neurodevelopmental disorders.

Disclosures: H.M. Ruby: None. **V.R. Riesgo:** None. **J. Willing:** None.

Poster

PSTR320: Motor Systems

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR320.04/A66

Topic: A.08. Development of Neural Systems

Support: Blazer Foundation
R01NS118066

Title: Construction of dual-fluorescent reporter stem cell lines to study human cortical motor neuron development with 3d cultures

Authors: *Z. CHEN[1], Y. YAN[2], S.-C. ZHANG[3], X.-J. LI[4];
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Abstract: Cortical motor neurons, long projection neurons located at deep layer of cerebral cortex, convey signals to muscles and control the movement of muscles. Degeneration of cortical motor neurons underlies debilitating motor neuron diseases including hereditary spastic paraplegias and amyotrophic lateral sclerosis. Mechanisms underlying the development and degeneration of cortical motor neurons in human cortex remain largely unknown, which requires a good model to study these neurons in vitro and in vivo. FEZF2 expression is detected in early forebrain progenitors and in their postmitotic progeny in deep cortical layers, while CTIP2 plays critical roles during neuron-differentiation and axonal extension in deep layer projection neurons of the cerebral cortex. To better understand and study the development of cortical motor neurons, we replaced stop codons of FEZF2 and CTIP2, two key transcriptional factors of cortical motor neurons, with green and red fluorescent genes zsGreen and tdTomato, respectively. After generation of FEZF2-zsGreen and CTIP2-tdTomato dual-fluorescent human embryonic stem cell (hESC) lines with CRISPR/Cas9 gene editing tools, the successful integration of the fluorescent genes were confirmed. To valid the reporter lines, we differentiated these reporter lines into cortical projections neurons. We then examined the expression of FEZF2 and CTIP2, and observed the co-labelling of these markers with the reporters. Moreover, both zsGreen and tdTomato fluorescent were able to recapitulate expression state of FEZF2 and CTIP2 at both the RNA and protein levels. Next, the double reporter cell lines were used for 3D brain organoid culture, allowing the maturation of the labelled cortical motor neurons. Finally, to study the connections between cortical motor neurons and their targets, spinal motor neurons, we co-cultured these cells by 3D printing of hESC-derived cortical and spinal motor neurons. The maturation and connections between these 3D-printed cells are under investigation. Taken together, our data demonstrate the construction of FEZF2-zsGreen /CTIP2-tdTomato hESC cell lines using CRISPR/Cas9-mediated gene editing. Furthermore, the reporter lines are successfully

applied in 3D culture systems, providing an innovative approach to study the development and degeneration of human cortical motor neurons.

Disclosures: Z. Chen: None. **Y. Yan:** None. **S. Zhang:** None. **X. Li:** None.

Poster

PSTR320: Motor Systems

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR320.05/A67

Topic: A.08. Development of Neural Systems

Title: Development of a Brain Organoid-on-Chip Platform for Neurotoxicity Testing

Authors: *T. POUMEYROL;
NETRI, Lyon, France

Abstract: In recent years, cerebral organoids have emerged as pivotal three-dimensional (3D) *in vitro* models of human cerebral cellular organization and development. However, their utility for compound toxicity screening is hindered by issues of reproducibility and scalability. To address this challenge, we combined cerebral organoid culture with a microfluidic device, NETRI's Duplex Well, to create a Brain Organoid-on-Chip platform. This integration enhances organoid reproducibility, predictability, and industrial transferability, crucial for applications in neurodevelopmental toxicity testing and drug screening. Our experimental strategy involves optimizing cortical organoid culture conditions within the microfluidic device, comprising two compartments separated by a porous membrane: a 3D culture chamber and a perfusion channel. By testing different organoid introduction time points and medium renewal methods, we established a robust protocol for maintaining cortical organoids in culture on-chip for up to four months. We next used this platform to develop scoring methodologies for cortical organoid characterization; one for quality control prior including an organoid in a protocol and the other for evaluation of compound toxicity. Based on this second scoring, we were able to establish a neurotoxicity prediction algorithm that we used to evaluate neurotoxicity of two compounds in acute and chronic exposures: biphenyl-2-ylamine (20-2000 µM) and vanillin (100-10000 nM). Our findings demonstrated that compared to cortical organoids grown in conventional support, on-chip organoids exhibited enhanced intra- and inter-batch reproducibility in terms of size, growth profile, and cytoarchitectural organization, across different cell lines. Preliminary neurotoxicological studies using this Brain Organoid-on-Chip platform, along with our scoring methods and prediction algorithm, revealed dose-response neurotoxicity for biphenyl-exposed conditions, highlighting neurotoxicological effects, while an absence of toxicity for vanillin exposures. These observations were consistent with previous *in vitro* studies, emphasizing the potential of this platform for predicting neurotoxicity. This Brain Organoid-on-Chip platform not only enables culture of cerebral organoids but also sets the stage for more complex applications, such as blood-brain barrier modeling and multi-organoid-on-chip platforms. Overall, our work offers a promising tool for enhanced neurotoxicity assessment and drug discovery.

Disclosures: T. Poumeyrol: None.

Poster

PSTR320: Motor Systems

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR320.06/A68

Topic: A.08. Development of Neural Systems

Support: NIH R37-HD081168

Title: Developmental changes in sensorimotor processing of the inferior olive in infant rats

Authors: *A. M. RICHARDSON[1], G. SOKOLOFF[2], M. S. BLUMBERG[1];
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Abstract: Distinguishing self-generated movements from other-generated movements is essential for animals to navigate their environment adaptively and successfully. The cerebellar system is especially sensitive to the distinction of the sensory consequences from self-generated (reafference) and other-generated (exafference) movements, as such an ability is critical for the development and maintenance of internal models. Such a distinction is only possible because reafference is accompanied by the production of motor copies (i.e., corollary discharges). Previous work from our lab, in the infant rat at postnatal days 8 and 12 (P8 and P12), has investigated how precerebellar nuclei the lateral reticular nucleus and the inferior olive (IO), and deep cerebellar nuclei differentially respond to reafference, exafference, and corollary discharge. These experiments suggested the same conclusion: that the infant IO fails to respond to externally generated sensory activity. Such a finding in the infant rat is at odds with what is known about the adult function of the IO—a structure understood as conveying unconditioned sensory stimuli to the cerebellum during learning. To resolve the apparent incongruity between the infant and adult IO, we recorded from the inferior olive and the interpositus nucleus of P12 rats of both sexes. During these recordings, rats produced self-generated movements through sleep-dependent myoclonic twitching before receiving proprioceptive stimulations of their forelimb ipsilateral to the IO recording site. Consequently, we found that the IO readily responds to corollary discharge produced by self-generated twitches but responds minimally to exafference from forelimb stimulations. Our ongoing investigation has extended to P20 to determine if sensorimotor activity in the IO exhibits into a more adult-like response profile. Thus, this study aims to reveal corollary discharge from the IO contributes to the development of cerebellar internal models.

Disclosures: A.M. Richardson: None. **G. Sokoloff:** None. **M.S. Blumberg:** None.

Poster

PSTR320: Motor Systems

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR320.07/A69

Topic: A.08. Development of Neural Systems

Support: R01 NS104344/NS/NINDS NIH HHS/United States

Title: Enhanced performance of amorphous silicon carbide microelectrode arrays in rat motor cortex

Authors: *P. HAGHIGHI[1], E. N. PAUL[4], B. S. STURGILL[6], J. ABBOTT[5], E. SOLIS[7], V. S. DEVATA[2], G. VIJAYAKUMAR[3], A. G. HERNANDEZ-REYNOSO[8], J. J. PANCRAZIO[2], S. F. COGAN[2];
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Abstract: Intracortical microelectrode arrays(MEAs) are devices that facilitate brain-machine communication. These devices can record neural signals at the level of single neurons. Clinically, they have applications in prostheses for restoring motor control and sensory perception. Despite their potential, MEA reliability for chronic recording has remained a challenge due to signal loss over time. Several factors have been identified contributing to this failure mechanism including device geometry, stiffness, etc. The degradation of the recording is associated with glial cell encapsulation of recording sites, contributing to the gradual loss of signals. Smaller cross-sectional areas have been linked to a demonstratable reduction in gliosis. This led us to develop MEAs with smaller cross-sectional areas using amorphous silicon carbide(aSiC), while maintaining sufficient stiffness for intracortical implantation without external support. To evaluate the chronic performance of aSiC multi-shank probes, we compared them with NeuroNexus(NNx) multi-shank MEAs. Both the aSiC and NNx devices have 4 shanks, each measuring 2mm in length. Each device accommodates a total of 16 channels, comprising four 200μm^2 recording sites per shank. Electrode sites are uniformly spaced 200µm apart along each shank, with shanks positioned 200 µm apart from each other. Notably, a key difference between the devices lies in their respective shank thicknesses: 8µm for aSiC and 15µm for NNx. In this study, we implanted adult female Sprague Dawley rats with the devices in the motor cortex. Seven rats were implanted with the a-SiC devices and five rats with NNx MEAs. Neural recordings were conducted weekly over 4 months with animals anesthetized with 2-3% isoflurane during each 10-minute recording session. Data was collected at 40kHz sampling frequency. The collected data were bandpass filtered, and a -4 standard deviations threshold was applied to discriminate single units, sorted by principal component analysis and manual validation. The percentage of channels that recorded at least one unit in a session was calculated to obtain the active electrode yield(AEY). The results demonstrated enhanced performance of the aSiC devices during the first week post-implantation, with 87% of the channels recording single unit activity, compared to 61% for NNx probes. The decline in the AEY of the aSiC devices to 51% over 16 weeks, compared to the NNx devices declining to 15%, highlights a notable

difference in their performance degradation.Our study highlights the enhanced chronic recording performance of a-SiC microelectrode arrays compared to commercially available NNx probes.

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Poster

PSTR320: Motor Systems

Location: MCP Hall A

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Program #/Poster #: PSTR320.08/A70

Topic: A.08. Development of Neural Systems

Support: NIH Grant K00NS120596
BWF PDEP

Title: Multidimensional anatomical atlas of developing cranial motor neurons in the embryonic mouse

Authors: *G. L. CARRILLO[1], L. FOZO[2], F. MENSCHING[3], E. C. ENGLE[4];
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Abstract: In vertebrates, movement of the eyes, face, head, and neck are controlled by paired cranial motor nerves. These efferent fibers are formed during embryonic development by distinct subpopulations of lower motor neurons. Synchronously, they migrate and organize into nuclei within the midbrain and hindbrain, while extending their axons to innervate cognate muscles. Failure of cranial motor neurons to undergo these precisely regulated developmental processes can lead to muscle paralysis or aberrant movements. Our current anatomical knowledge of cranial nerve development primarily relies on reconstruction of two-dimensional images generated by traditional histological methods. Such methods inherently create biased sampling of neurons and reduces visualization of microstructural details. In this study, we sought to create a detailed multidimensional anatomical atlas of cranial motor neuron development in the embryonic mouse (X, Y, Z, time). We combined transgenic reporter mice backcrossed to different genetic backgrounds (129S1, C57BL/6J, and mixed) with whole-embryo clearing and immunolabeling approaches to label developing cranial motor neurons, their axons, and target muscles from embryonic ages E9.5 to E18.5. We employed 3D imaging technology (point and line-scanning confocal, and light sheet microscopy), and performed qualitative and quantitative analysis using 3D modular image analysis software, virtual reality, and deep learning algorithms to assess cranial motor neuron migration, apoptosis, nerve outgrowth, branching patterns, and muscle growth and innervation. Together, these data provide highly refined neuroanatomical definition of developing cranial nerves and muscles, including novel insight into permanent

versus transient nerve branches, while conserving the original spatial resolution of the whole, intact embryo. Moreover, the atlas provides comparison of the developing neuroanatomy on commonly used mouse genetic backgrounds, serving as a valuable tool for researchers studying both cranial nerve and muscle development in health and disease.

Disclosures: G.L. Carrillo: None. **L. Fozo:** None. **F. Mensching:** None. **E.C. Engle:** None.

Poster

PSTR320: Motor Systems

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR320.09/A71

Topic: A.08. Development of Neural Systems

Title: Examining the impact of embryonic fluoride exposure on zebrafish behavior

Authors: *T. M. GALAVOTTI[1], K. M. ACKERMAN[2];
[1]High Point Univ., High Point, NC; [2]Med. Sci., High Point Univ., High Point, NC

Abstract: Fluoride (F) is the ionic form of the element, fluorine. F is known to enhance enamel remineralization and inhibit acid production by plaque bacteria which helps limit the prevalence of dental caries (cavities). To supplement dental care, multiple countries have implemented a community water fluoridation plan. While this community water fluoridation plan might be helpful in the dental sphere, higher concentrations of F can have harmful effects, such as neurotoxicity, which is especially harmful during development. F is also highly permeable to important membranes, like the placenta and the blood-brain barrier which makes its ability to impact neurodevelopment more pressing. Systematic reviews suggest that "exposure to fluoride at a level of more than 2 mg/L in drinking water may result in impaired cognitive outcomes among children" (Gopu et. al, 2022). Another review states, "there is little doubt that developmental neurotoxicity is a serious risk associated with elevated fluoride levels" (Grandjean, 2019). While some research has been performed to demonstrate an association between F exposure during development and cognitive deficits, little research has been done into the behavioral changes that F causes or the possible genetic manipulation that F engages in. We have found an increase in anxiety-like behaviors, skeletal malformations, and pigmentation loss through behavioral assays and observational methods. Further data collection is in progress, but we expect to see changes in anxiety like behaviors through changes in cholinergic signaling which can be analyzed via matched behavioral assays and gene expression changes.

Disclosures: T.M. Galavotti: None. **K.M. Ackerman:** A. Employment/Salary (full or part-time):; High Point University.

Poster

PSTR320: Motor Systems

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR320.10/A72

Topic: A.08. Development of Neural Systems

Support: KAKENHI 24K02117
KAKENHI 24H01225
KAKENHI 23H04213

Title: Segment-specific axon guidance by Wnt/Fz signaling diversifies motor commands in Drosophila larvae

Authors: S. TAKAGI[1], ***A. NOSE**[2];
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Abstract: Functional diversification of homologous neuronal microcircuits is a widespread feature observed across brain regions as well as across species, while its molecular and developmental mechanisms remain largely unknown. We address this question in *Drosophila* larvae by focusing on segmentally homologous Wave command-like neurons, which diversify their wiring and function in a segment-specific manner. Anterior Wave (a-Wave) neurons extend axons anteriorly and connect to circuits inducing backward locomotion, whereas posterior Wave (p-Wave) neurons extend axons posteriorly and trigger forward locomotion. Here, we show that Frizzled receptors DFz2 and DFz4, together with the DWnt4 ligand, regulate the segment-specific Wave axon projection. DFz2 knock-down (KD) not only reroutes Wave axons to posterior neuromeres but also biases its motor command to induce forward instead of backward locomotion as tactile response. Thus, segment-specific axon guidance diversifies the function of homologous command neurons in behavioral regulation. Since control of anterior-posterior (A-P) axon guidance by Wnt/Fz-signaling is evolutionarily conserved, our results reveal a potentially universal molecular principle for formation and diversification of the command system in the nerve cord. Furthermore, this work indicates that sensorimotor transduction can be rerouted by manipulating a single gene in a single class of neurons, potentially facilitating the evolutionary flexibility in action selection.

Disclosures: S. Takagi: None. **A. Nose:** None.

Poster

PSTR320: Motor Systems

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR320.11/A73

Topic: A.08. Development of Neural Systems

Title: Exploring myelinating glial plasticity at motor exit point transition zones

Authors: T. DALLO[1], *L. FONTENAS[2];
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Abstract: The nervous system is divided into two separate, yet connected domains: the central nervous system (CNS) and peripheral nervous system (PNS), in which distinct cell types often carry out similar biological functions. For example, oligodendrocytes are restricted to the CNS and Schwann cells are limited to the PNS, and both glial subtypes function to myelinate axons. Demyelinating diseases (e.g. multiple sclerosis) commonly affect half of the nervous system, while the other half remains healthy and myelinated. Communication between the CNS and the PNS is possible through transition zones (TZ) - specialized gaps in the CNS/PNS interface - where central and peripheral neural tissue meet. We recently characterized a previously unknown population of glial cells named motor exit point (MEP) glia, that are born in the spinal cord and migrate into the PNS to myelinate motor root axons. Using larval zebrafish, we investigated from which specific neural tube precursors MEP glia are specified, and how they exit the neural tube and migrate onto peripheral motor axons. In these studies, we showed that MEP glia originate from *nkx2.2a*$^{+}$/*olig2*$^{+}$ radial glial precursors and require *foxd3* to delaminate from the lateral floor plate and exit the spinal cord via MEP TZs. Here, we show that like Schwann cells, MEP glial development depends on axonally-derived neuregulin 1 (nrg1) type III. MEP glia possess central/peripheral hybrid features and molecular profiles. Conveniently, they are located at the borders of the spinal cord, leading us to hypothesize that they could function in both halves of the nervous system. We previously demonstrated the presence of oligodendrocytes along motor axons upon perturbation, but the integrity and maintenance of these ectopic myelin sheaths have yet to be studied. We are now investigating the feasibility of diverting healthy myelinating glia to the other half of the nervous system under physiological and demyelination conditions. Using previously described *nrg1* zebrafish mutants that lack MEP glia at motor nerve roots, we show that oligodendrocytes ectopically migrate onto and myelinate peripheral motor axons by 3 days post-fertilization (dpf). Conversely, to test whether peripheral glia can contribute to repairing the lesioned CNS, we have generated and validated a spinal cord demyelination model that takes advantage of the nitroreductase chemoablation system.These experiments will advance our understanding of how myelin-forming glial cells segregate at the CNS/PNS boundary in physiology, while remaining plastic upon perturbations.

Disclosures: T. Dallo: None. **L. Fontenas:** None.

Poster

PSTR321: Ligand-Gated Receptors and Ion Channels: Gaba and Glycine

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR321.01/A74

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

Support: NIH Grant R01NS11737

Title: Tonic Inhibition Mediated by $GABA_AR$-α4 Receptors in Sparse Coding in the Dentate Gyrus

Authors: *M. KRUSH, T. MCLEAN, C. CHATZI, E. SCHNELL, G. L. WESTBROOK; Vollum Inst., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: The dentate gyrus (DG), the information entry zone in the hippocampal circuit, receives and integrates contextual and spatiotemporal information from the entorhinal cortex. It encodes these inputs as a "sparse" network with few granule cells active at any one time. This network property provides a high signal-to-noise ratio for representations of incoming activity and facilitates pattern separation, a component of memory formation. However, the cellular mechanisms underlying sparse coding and pattern separation are not well defined. We hypothesize that this sparsity is partially mediated by tonic inhibition of granule cells, mediated by the actions of ambient GABA at high affinity α4-containing $GABA_A$ receptors ($GABA_AR$-α4). To explore this issue, we pharmacologically manipulated extracellular GABA levels in wild type mice using the non-specific GABA uptake blocker NO-711 and used the selective $GABA_AR$-α4 receptor agonist THIP to exogenously activate these receptors. Granule cell activity was assessed by staining for the immediate early gene *cFos*. There were significantly fewer cFos+ granule cells in THIP treated mice compared to saline controls (35% reduction, $p<0.05$), or NO-711 (8% reduction, ns), consistent with $GABA_AR$-α4 contributing to baseline (tonic) inhibition in the DG. To examine the role of $GABA_AR$-α4 receptors *in vivo*, we have also developed viral and genetic tools to selectively knockout $GABA_A$-α4 in the DG using conditional (floxed) GABAA-$\alpha4^{fl/fl}$ mice, including viral Cre constructs (nuclear Cre or FosTRAP Cre) to knockdown $GABA_A$-α4 in subsets of granule cells, as well as granule cell-selective knockouts using POMC-Cre mice. These approaches will allow us to assess neural activity (cFos+ cells) in $GABA_A$-α4-expressing and -deleted cells in the same animal. Our experiments test the consequences of disrupted tonic inhibition at baseline and following physiological stimuli (voluntary exercise, environmental enrichment) to clarify a stereotyped but not fully understood feature of information encoding in the DG.

Disclosures: M. Krush: None. **T. McLean:** None. **C. Chatzi:** None. **E. Schnell:** None. **G.L. Westbrook:** None.

Poster

PSTR321: Ligand-Gated Receptors and Ion Channels: Gaba and Glycine

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR321.02/A75

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

Support: Academy of Finland (330776, 336376, 318879, 355256)
University of Oslo Convergence Environment (4MENT)

EBRAINS partnering project (SubSchiz)
CSC Finland (project 2003397)
UNINETT Sigma2 (project NN9529K)

Title: Modelling of GABAB-receptor activity in pre- and postsynaptic domains and their effects on pyramidal cells

Authors: *T. MÄKI-MARTTUNEN[1,2], J. KISMUL[1], K. PAJO[3], T. MANNINEN[1], J. M. SCHULZ[4], G. T. EINEVOLL[5], M.-L. LINNE[1], O. A. ANDREASSEN[6], J. HELLGREN KOTALESKI[7];
[1]Tampere Univ., Tampere, Finland; [2]University of Oslo, Oslo, Norway; [3]Neurosci., Karolinska Inst., Stockholm, Sweden; [4]Dept. of Biomedicine, Univ. of Basel, Basel, Switzerland; [5]Norwegian Univ. Life Sci., Aas, Norway; [6]Oslo Univ. Hosp. - Ulleval, Oslo, Norway; [7]Computer Sci., KTH Royal Inst. of Technology: Kungliga Tekniska Hogskolan, Stockholm, Sweden

Abstract: GABAB receptors (GABABRs) are a crucial regulator of neural activity. Although they have a hypothesized role in many basic neuronal functions as well as mental disorder symptomology, there is a lack of biophysically and biochemically detailed models of these receptors that are capable of revealing how they mediate neuronal inhibition. Here, we developed a computational model for the activation of GABABRs and their coupling with G protein-coupled inwardly rectifying potassium (GIRK) channels and voltage-gated Ca^{2+} channels. We fit our model to both pre- and postsynaptic electrophysiological data from pyramidal cells to ensure the generality of our modelling framework. We compared the predictions of our model with experimental data on postsynaptic effects of GABABRs on layer V pyramidal cell firing activity. We also simulated the combined effects of presynaptic and postsynaptic GABABR blockage on pyramidal cell activity and showed that these were largely and robustly cumulative. Finally, we reproduced the effects of a knock-out of RGS7 (a G protein signaling protein) on CA1 pyramidal cell electrophysiological properties and dissected the mechanistic source of these effects. This shows the potential of our model in generating insights on genetic manipulations of the GABABR system. Our model thus provides a flexible tool for biochemically and biophysically detailed simulations of various aspects of GABABR activation that can reveal both foundational electrophysiological properties of neuronal dynamics and mental disorder-associated traits and treatment options.

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Poster

PSTR321: Ligand-Gated Receptors and Ion Channels: Gaba and Glycine

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR321.03/A76

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

Title: Spinal extrasynaptic GlyR a1 subunits regulate startle response and motor coordination

Authors: *S. WEI[1,2], H.-L. PAN[3], Y. XU[4], D. M. LOVINGER[1], L. ZHANG[1];
[1]Lab. for Integrative Neurosci., NIAAA/NIH, Rockville, MD; [2]University of Pittsburgh, Pittsburgh, PA; [3]Univ. of Texas Houston Med. Ctr., Houston, TX; [4]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The α1 subunit-containing glycine receptors (GlyRα1s) are the most abundant inhibitory ligand-gated ion channels in the spinal cord and brainstem at the adult stage, where they mediate the majority of inhibitory neurotransmission. GlyRα1 deficiency or malfunction leads to exaggerated startle response and motor impairment in human and animals. However, little is known about the cell-type specific mechanisms underlying GlyRα1-mediated *in vivo* effects. To address this question, we selectively depleted GlyRα1 from $GlyT2^+$ and $CamK2α^+$ neurons in mice. The mRNA signals of all three genes are colocalized in spinal cord and brain stem slices in normal mice. Homozygous mutation disrupted the colocalization of GlyT2 with GlyRα1 mRNA signal and reduced the expression of GlyRα1 protein in spinal and brainstem tissues. As a result, both homozygous and heterozygous mice with $GlyT2^+$-cell-selective GlyRα1 deficiency showed impaired balance and coordination skills. Global GlyRα1 deficiency increased acoustic-induced startle response. In contrast, both homozygous and heterozygous GlyT2-GlyRα1 deficient mice decreased the level of startle response to acoustic stimulations. The similar reduction was also observed in the transgenic mice with inducible GlyRα1 deficiency in $CamK2a^+$ cells. To our surprise, depletion of GlyRα1 from GlyT2 neurons selectively reduced the amplitude of Gly-activated current without significantly altering glycinergic IPSCs and glutamatergic EPSCs. Taken together, these results suggest differential roles of GlyRα1 in the balance of excitatory and inhibitory circuits in the spinal cord and brainstem. Future investigations will measure synaptic transmission and Gly-activated currents in spinal neurons without and with GlyRα1 deletion. It is likely that GlyRα1 subunits expressed in non-synaptic sites of spinal interneurons contribute to the regulation of motor function and startle response. The extrasynaptic GlyRα1 may be a potential therapeutic target for GlyR-involved neurological diseases.

Disclosures: S. Wei: None. **H. Pan:** None. **Y. Xu:** None. **D.M. Lovinger:** None. **L. Zhang:** None.

Poster

PSTR321: Ligand-Gated Receptors and Ion Channels: Gaba and Glycine

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR321.04/A77

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

Support: VA Merit Review Award - 2 I01 BX002745-06A2

Title: Gaba-b receptors are activated following gaba transaminase inhibition with vigabatrin and during spontaneous neural activity induced by 4-aminopyridine

Authors: G. S. NEWKIRK[1], A. NOLAN[2], ***C. RANSOM**[3];
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Abstract: GABA-B receptors are activated following GABA transaminase inhibition with vigabatrin and during spontaneous neural activity induced by 4-Aminopyridine Gregory S. Newkirk[1,2], Alicia Feichtinbiner[1,4], Karinn Systma[1,4], Amber Nolan[1,4], Christopher B. Ransom[1,2,31]Epilepsy Center of Excellence, VA Puget Sound, Seattle, WA 98108; Depts of [2]Neurology, [3]Physiology and Biophysics, and [4]Pathology, University of Washington, Seattle, WA

Abstract*In vitro* models of hyperexcitability, including the K+ channel blocker 4-aminopyridine (4AP) and zero Mg^{2+} solutions, have been valuable tools to study neuronal mechanisms related to seizures and antiepileptic drugs. We made current clamp recordings from cortical (layer IV/V) and hippocampal (CA1) pyramidal neurons in mouse brain slices during superfusion of 4AP or zero Mg^{2+} solutions. Both cortical and hippocampal neurons showed marked increase in excitatory synaptic currents and irregular spiking during 4AP or zero Mg^{2+} exposure. This network hyperexcitability was suppressed by the GABA-B receptor agonist baclofen and the effect of baclofen was reversed by the GABA-B receptor antagonist CGP55485 (CGP, 20 μM) and the GIRK channel blocker Ba^{2+} (100 μM), results that indicate GABA-B receptors suppress hyperexcitability in these models. Pretreatment of slices with the GABA transaminase inhibitor vigabatrin markedly suppressed *in vitro* activity produced by 4AP or zero Mg^{2+} and this suppression was reversed by CGP and Ba^{2+}, indicating that vigabatrin suppresses *in vitro* hyperexcitability via activation of GABA-B receptors. Additionally, 4AP exposure generated slow, pseudoperiodic hyperpolarizations in hippocampal neurons that occurred at frequency of 0.043 +/- 0.01 Hz (mean +/- S.D.) with amplitudes of -5.0 +/- 1.2 mV and decay time constant (τ) of 497 +/- 48 ms. These robust, periodic hyperpolarizations were inhibited by the GABA-B receptor blocker CGP55485 and the GIRK channel blocker Ba^{2+}, indicating that they are due to activation of postsynaptic GABA-B receptors. Overall, our data show that GABA-B receptors potently suppress *in vitro* epileptiform activity in both cortex and hippocampus, establish that vigabatrin actions are dependent on GABA-B receptors, and demonstrate that GABA-B receptors are activated in CA1 neurons during spontaneous *in vitro* epileptiform activity. Although GABA-B receptors are reported to aggravate seizures in some epilepsy syndromes, our results suggest that GABA-B receptors could be effective therapeutic targets in some cases, including those epilepsy syndromes that respond well to vigabatrin therapy such as infantile spasms.

Disclosures: G.S. Newkirk: None. **A. Nolan:** None. **C. Ransom:** None.

Poster

PSTR321: Ligand-Gated Receptors and Ion Channels: Gaba and Glycine

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR321.05/A78

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

Title: Effective Control of Serial Exposure to Agonists and Modulators is Key to High Throughput Ligand Gated Patch Clamp Assays

Authors: *A. YEHIA[1], **S. PROANO**[2];
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Abstract: Modulators of ligand-gated ion channel (LGIC) activity are being actively developed by a number of leading pharmaceutical companies. Although patch clamp assays remain the gold standard for determining functional compound effects on these targets, they pose unique challenges due to the need for accurate temporal control of agonist and compound application. With the need to increase throughput in ligand-gated assays, currently available automation in patch clamping mostly involves platforms with key shortcomings, such as an inherent inability to precisely control effective target/compound exposures. Here we present results from complex ligated gated assays facilitated by a unique microfluidic-based platform with effective and fast compound exchange and automatic continuous wash. The data includes case studies from Glutamate, nicotinic, and GABA receptors.

Disclosures: A. Yehia: None. **S. Proano:** None.

Poster

PSTR321: Ligand-Gated Receptors and Ion Channels: Gaba and Glycine

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR321.06/Web Only

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

Support: CIHR Foundation Grant (FDN-154312)
Dr. Kirk Weber Award in Anesthesia

Title: A novel peptide to reduce sevoflurane-mediated excess cell-surface expression of α5GABA$_A$ receptors

Authors: *M. YU[1], A. ARIZA[1], D.-S. WANG[1], L. KAUSTOV[2], B. A. ORSER[3];
[1]Physiol., Univ. of Toronto, Toronto, ON, Canada; [2]Anesthesia, Sunnybrook Hlth. Sci. Ctr., Toronto, ON, Canada; [3]Dept. of Anesthesiol. & Pain Med., Univ. of Toronto, Toronto, ON, Canada

Abstract: Cognitive deficits occur frequently in older patients after anesthesia and surgery and are associated with poor long-term outcomes. Unfortunately, there are no pharmacological strategies to treat or prevent such cognitive deficits. We previously showed that anesthetic drugs cause a persistent increase in cell-surface expression of α5GABA$_A$Rs in hippocampal neurons through mechanisms that depend on astrocyte-neuron crosstalk. The resulting increase in tonic

inhibitory current in neurons contributes to post-anesthetic cognitive deficits. Thus, reducing cell-surface expression of α5GABA$_A$Rs may mitigate postoperative cognitive deficits. α5GABA$_A$Rs are tethered to extrasynaptic region of neurons via the cytoskeletal anchoring protein radixin. Based on this information, we postulated that disrupting the interaction between radixin and α5 subunits may reduce cell-surface expression of α5GABA$_A$Rs through increased endocytosis. To test this hypothesis, we designed an inhibitory peptide that mimicked the α5-subunit binding site on radixin. The peptide was conjugated with a TAT-sequence to enhance cell penetrance. We first determined that the TAT-peptide prevented the interaction between α5 subunits and radixin using mouse hippocampal tissue and co-immunoprecipitation techniques. Next, we studied whether the TAT-peptide modified baseline levels of α5GABA$_A$Rs in neurons using immunocytochemistry and immunofluorescent staining techniques. This experiment showed that cell-surface expression of α5GABA$_A$Rs was unaltered by TAT-peptide at baseline compared to a negative control TAT-scrambled peptide. Then, to determine whether the TAT-peptide reversed anesthetic-mediated excess cell-surface α5GABA$_A$R expression, *in vitro* mouse cortical astrocytes were exposed to sevoflurane (2.4% for 1 h) and 2 h later, the sevoflurane-conditioned astrocyte media was transferred to cultured mouse hippocampal neurons. Sevoflurane-conditioned astrocyte media resulted in a 1.5-fold increase in cell-surface expression of α5GABA$_A$Rs in the neurons (n=147 regions of interest, $p<0.0001$). However, cotreatment with the TAT-peptide (0.1 μM) did not reverse excess cell-surface expression of α5GABA$_A$Rs (n=148–150 regions of interest, $p=0.25$) when compared to TAT-scrambled peptide. Our results confirmed that sevoflurane increased cell-surface expression of α5GABA$_A$Rs, but this increase was not affected by the TAT-peptide. Ongoing studies will examine dose- and time-dependent effects of the TAT-peptide on synaptic versus extrasynaptic localization of α5GABA$_A$Rs receptors.

Disclosures: M. Yu: None. **A. Ariza:** None. **D. Wang:** None. **L. Kaustov:** None. **B.A. Orser:** A. Employment/Salary (full or part-time):; University of Toronto; Sunnybrook Health Sciences Centre. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CIHR Foundation Grant (FDN-154312). C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Cogstate Ltd (New Haven, CT, USA). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Canadian patent (2,852,978); US Patents (9,517,265 and 10,981,954). F. Consulting Fees (e.g., advisory boards); Chair of the Board of Trustees of the International Anesthesia Research Society (San Francisco, CA, USA); co-director of the Perioperative Brain Health Centre (Toronto, Ontario, Canada).

Poster

PSTR321: Ligand-Gated Receptors and Ion Channels: Gaba and Glycine

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR321.07/A79

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

Support: NIH Grant R01MH114908
NINDS Grant T32NS086749
University of Pittsburgh School of Medicine Research Funds

Title: To the synapse and beyond: characterizing the regulatory mechanisms for α5 $GABA_A$receptor distribution in hippocampal neurons

Authors: *J. L. NUWER[1], S. J. MOSS[2], T. C. JACOB[1];
[1]Pharmacol. & Chem. Biol., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [2]Neurosci., Tufts Univ., Boston, MA

Abstract: In the adult brain, GABA type A receptors ($GABA_ARs$) generate fast inhibitory signals to dampen and control neuronal activity at the network and cellular levels. The function and pharmacology of this heteropentameric receptor depends on subunit composition and arrangement, which is regulated by the spatial, temporal, and subcellular expression pattern of the 19 $GABA_AR$ subunits. α5 subunit-containing $GABA_ARs$ (α5 $GABA_ARs$) are a unique receptor subtype of particular interest due to their enriched hippocampal expression and key roles in neuronal development, synaptic plasticity, and cognitive function. While proper α5 $GABA_AR$ surface distribution (synaptic vs extrasynaptic localization) and activity-dependent reorganization are crucial for these roles, the regulatory mechanisms are poorly defined. Like α1-3 $GABA_ARs$, α5 $GABA_ARs$ exhibit receptor clustering at synaptic sites due to direct interactions between the α subunit and the inhibitory postsynaptic scaffold gephyrin. Unlike other $GABA_ARs$, however, α5 $GABA_ARs$ also form receptor clusters at extrasynaptic sites due to direct interactions between the α5 subunit and the actin-binding protein radixin. While the gephyrin binding domain is known, the radixin binding domain remains elusive. Surprisingly, the reported radixin binding domain exists in a region of high homology between all $GABA_AR$ α subunits (AA 342-357). Conversely, the gephyrin binding domain exists in a region of much lower homology (AA 370-385). Our antibody-based proximity ligation and immunoprecipitation experiments assessing α5/radixin interaction in primary hippocampal neurons suggest that the radixin binding domain exists in an alternate region. We propose that this region, which overlaps with the gephyrin binding domain and contains two α5 phospho-sites (S374 and S406), also contains a novel radixin binding domain that imparts subunit specificity. Further, we hypothesize that the phosphorylation state of S374 acts as a "switch" to control α5 $GABA_AR$ association with radixin vs gephyrin scaffolds, as phosphorylation is a key regulator of other $GABA_AR$/scaffold interactions. Here we will define the radixin binding domain, identify the role of α5 $GABA_AR$ phospho-dependent regulation in receptor/scaffold interactions, and assess the impact of impaired radixin binding on neuronal development and inhibitory transmission.

Disclosures: J.L. Nuwer: None. **S.J. Moss:** None. **T.C. Jacob:** None.

Poster

PSTR321: Ligand-Gated Receptors and Ion Channels: Gaba and Glycine

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR321.08/B1

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

Support: FWF Grant I3778
FWF Grant W1232

Title: Probes for the Heterogeneity of Muscimol Binding Sites in Rat Brain

Authors: *P. SCHOLZE, M. ERNST;
Ctr. for Brain Res., Med. Univ. of Vienna, Wien, Austria

Abstract: The plant-based alkaloid muscimol is a potent agonist of inhibitory $GABA_A$-neurotransmitter-receptors. $GABA_A$ receptors are a heterogenous family of pentameric complexes, with 5 out of 19 subunits assembling around the central anion pore. Muscimol is considered to bind to all receptor subtypes at the orthosteric drug binding site at the β+ and the α- interface. In one of our recent publications, we observed that the antipsychotic drugs clozapine (CLZ), loxapine (LOX) and chlorpromazine (CPZ) although exerting functional inhibition on multiple $GABA_A$ receptor subtypes showed diverging results in displacing 3H-mucimol. While a complete displacement could be observed in hippocampal membranes by bicuculline (BIC), and no displacement with CPZ, the compounds CLZ and LOX could only incompletely compete with the radioligand. In addition, the dose-response curves displayed a non-sigmoidal complex form, indicating that they are not following a standard one-site binding pharmacology. In the current study we now aimed to investigate more extensively this heterogeneity of bicuculline sensitive muscimol sites in rat brain. We tested membranes from four different brain regions (hippocampus, cerebellum, thalamus and striatum) and incubated them with 3H-muscimol and the four different compounds BIC, LOX, CLZ and CPZ. We observed a unique pharmacology of each tested compound in the studied brain regions. Combining two of the tested ligands suggests that in striatum all CLZ sites are contained in the pool of LOX sites, while the CPZ sites may in part be non- overlapping with LOX sites. Experiments on recombinantly expressed receptors indicate, that BIC can displace 3H-muscimol from all tested receptors, while LOX and CLZ more potently compete with 3H-muscimol in α4β2 compared to α1β2 or α6β2-containing receptors, suggesting a subtype selectivity. Our experimental findings are supported by docking analysis, designed to find structural correlates of the observed diversity of muscimol sites that are present in the samples from brain tissue and recombinantly expressed $GABA_A$ receptor subunit combinations.These findings indicate that 3H-muscimol binding sites in rat brain are more heterogenous than previously thought, with different populations of receptors, which are CPZ, LOX or CLZ sensitive or insensitive. These binding sites show a varying distribution in different rat brain regions.

Disclosures: P. Scholze: None. **M. Ernst:** None.

Poster

PSTR321: Ligand-Gated Receptors and Ion Channels: Gaba and Glycine

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR321.09/B2

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

Support: NIMH grants R01 MH123748
P50 MH122379
F30 MH126548

Title: Delta-containing gabaa receptors on parvalbumin interneurons modulate neuronal excitability and network dynamics in the mouse medial prefrontal cortex

Authors: *X. LU[1], P. LAMBERT[2], H. SHU[3], C. F. ZORUMSKI[4], S. J. MENNERICK[5]; [1]Washington Univ. In St. Louis, Saint Louis, MO; [3]Dept Psychiatry, Box 8134, [2]Washington Univ. In St Louis, Saint Louis, MO; [4]Psychiatry, Washington Univ. Med. Sch., Saint Louis, MO; [5]Psychiatry, Washington Univ. Sch. of Med., St. Louis, MO

Abstract: In the medial prefrontal cortex (mPFC), fast-spiking parvalbumin (PV) interneurons regulate excitability and microcircuit oscillatory activity important for cognition. Although PV interneurons inhibit pyramidal neurons, they themselves express the δ subunit of $GABA_A$ receptors important for slow inhibition. However, the specific contribution of δ-containing $GABA_A$ receptors to the function of PV interneurons in the mPFC is unclear. We explored cellular, synaptic, and local-circuit activity in PV interneurons and pyramidal neurons in mouse mPFC after selectively deleting the δ subunit in PV interneurons (cKO mice). In current-clamp recordings cKO PV interneurons exhibited a higher frequency of action potentials and higher input resistance than wild type (WT) PV interneurons. Picrotoxin increased firing and GABA decreased firing in WT PV interneurons but not in cKO PV interneurons. The δ-preferring agonist THIP reduced spontaneous inhibitory postsynaptic currents in WT pyramidal neurons but not in cKO pyramidal neurons. In WT slices, depolarizing the network with 400 nM kainate increased firing of pyramidal neurons but had little effect on PV interneuron firing. By contrast, in cKO slices kainate recruited PV interneurons at the expense of pyramidal neurons. At the population level, kainate induced broadband increases in local field potentials in WT but not cKO slices. These results on cells and the network can be understood through increased excitability of cKO PV interneurons. In summary, our study demonstrates that δ-containing $GABA_A$ receptors in mPFC PV interneurons play a crucial role in regulating their excitability and the phasic inhibition of pyramidal neurons, elucidating intricate mechanisms governing cortical circuitry.

Disclosures: X. Lu: None. **P. Lambert:** None. **H. Shu:** None. **C.F. Zorumski:** None. **S.J. Mennerick:** None.

Poster

PSTR321: Ligand-Gated Receptors and Ion Channels: Gaba and Glycine

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR321.10/B3

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

Support: R01AG073133 to AL (Agenor Limon)
R01AG070255 to AL (Agenor Limon)

Title: Brain regional differences in AMPA, GABA and glycine synaptic receptors from mus musculus.

Authors: *L. SÁNCHEZ SÁNCHEZ[1], B. MILLER[1], J. FOREMAN[1], M. ORTIZ[3,4,5], I. E. CISNEROS[3,6,5], A. LIMON[2,1];
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Abstract: Mouse animal models are widely used as experimental tools in the research of different diseases, including psychiatric, cognitive, neurodegenerative, and infectious diseases. In this sense, brain from murine models is widely studied in the proteomics field, presenting differences along the regions. However, even with that information, the diversity of functionality of neurotransmitter receptors across brain regions remain elusive. Using electrophysiology of mice synaptosomes from prefrontal cortex, hippocampus, striatum, olfactory bulb, cerebellum, and medulla we aimed to investigate the differences between these regions in the signals of GABA, AMPA and glycine receptors, which are major drivers of synaptic excitation (E) and inhibition (I) in the nervous system. Electrophysiological E/I ratios were assessed by micro transplantation of synaptic membranes (MSM). We found that GABA receptors peak amplitude was significantly lower in hippocampus compared with olfactory bulb and striatum. The same tendency that was observed for AMPA receptors, were the amplitude of AMPA receptors in hippocampus was lower than in medulla and striatum samples. The E/I ratio was significantly higher in mice medulla samples compared to olfactory bulb suggesting a distinct set point for excitation to inhibition balance across brain regions. Understanding the differences in the functional status of synaptic receptors and their relationship with the synapto-proteome in different mice brain areas is a necessary step to translate those differences to human research in different neuropathological conditions.

Disclosures: L. Sánchez Sánchez: None. **B. Miller:** None. **J. Foreman:** None. **M. Ortiz:** None. **I.E. Cisneros:** None. **A. Limon:** None.

Poster

PSTR321: Ligand-Gated Receptors and Ion Channels: Gaba and Glycine

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR321.11/B4

Topic: A.08. Development of Neural Systems

Support: PE501082200-2023-PROCIENCIA

Title: Developing changes in the chloride cotransporters at molecular level could explain the shift in the effect of GABAergic synaptic transmission in the piriform cortex of infant rats.

Authors: *C. BECERRA FLORES[1], C. MEDINA-SALDIVAR[2,3], G. E. PARDO[2,3], L. PACHECO[1,3];
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Abstract: Background: The effect of GABAergic synaptic transmission in the anterior piriform cortex (aPC) of infant rats changes with age, which is characterized by a shift in the GABA reversal potential (E_{GABA}) from depolarizing to hyperpolarizing electrophysiological values in the aPC pyramidal cells between the first and second postnatal weeks of life, which could explain the ability of infants to learn the maternal odor during the sensitive period for attachment. These electrophysiological developmental changes in E_{GABA} could be attributed to alterations in intracellular and intracellular chloride concentration, driven by molecular changes in the expression levels of chloride transporters KCC2 and NKCC1. In this study, we investigated the expression levels of both cotransporters in male and female rats, considering the sexual dimorphism in protein expression of NKCC1 and KCC2 observed in other brain structures. **Methods:** Male and female Sprague Dawley rat brains were dissected at different postnatal ages: Postnatal days (DPN) 5-6, 7-8, 11-12, 13-14, 15-16, 17-18, and, 19-20, 21-22 (weaning day), with adult male and female brains respectively serving as controls. Gene expression levels were assessed using RT-qPCR and Western Blot analysis. Sexual dimorphism profiles were compared relative to adult males. **Results:** In male rats, both mRNA and protein expression of KCC2 and NKCC1 reached adult levels by DPN 15-18, with notable gene expression differences observed only at DPN 19-22. In female rats, NKCC1 gene and protein expression maintained an adult profile from DPN 11-14, while KCC2 gene expression peaked at DPN 11-14, decreasing significantly in subsequent days, and then returned to an upregulation until reaching the adult profile. Additionally, both cotransporters exhibited a sexually dimorphic expression profile with females displaying higher expression levels compared to males. **Conclusions:** Our findings suggest that the developing switch of E_{GABA} in the aPC may be supported by an increased KCC2 expression, mostly in neurons, which begins to maintain low levels of intracellular chloride from DPN 11-14. However, the increased expression of NKCC1 during the same postnatal period suggests that the regulation of NKCC1 expression levels and its role in maintaining intracellular chloride concentration may be influenced by the early upregulation of KCC2. Furthermore, the role of NKCC1 could be extended beyond neuronal populations to include functions in various non-neuronal populations of the olfactory cortex during early postnatal development.

Disclosures: C. Becerra Flores: None. **C. Medina-Saldivar:** None. **G.E. Pardo:** None. **L. Pacheco:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.01/B5

Topic: B.05. Synaptic Plasticity

Support: NS130108
NS085164

Title: Drosophila Prospero links neuromuscular development, homeostatic control of neurotransmission, and locomotion

Authors: *D. ZWIEFELHOFER[1], B. MALLIK[2], K. M. LEMBKE[3], C. FRANK[1];
[1]Univ. of Iowa, Iowa City, IA; [2]Univ. of Iowa, IOWA CITY, IA; [3]Biol. and Mol. Sci., George Fox Univ., Newberg, OR

Abstract: Homeostatic synaptic plasticity stabilizes neuronal and circuit activities. Unstable neuronal activity may underlie diseases associated with unstable neural function, like forms of epilepsy, ataxia, migraine, and myasthenia. The *Drosophila melanogaster* neuromuscular junction (NMJ) is valuable synapse to model how synapses stabilize their outputs despite perturbations. At the NMJ, impaired muscle sensitivity to neurotransmitter is offset by an increase in presynaptic neurotransmitter release. Our lab and others have identified several molecules and signaling modalities needed for this process. A surprising finding has emerged from our approach: even though homeostatic signaling is normally a robust process, glutamate receptor impairment at the NMJ can render both the synapse and the entire muscle vulnerable to severe developmental dysfunction. One example arises from examination of the neuronal determination factor Prospero. Partial loss of *prospero* gene function is known to impair neuronal differentiation and muscle innervation without severely affecting muscle development or NMJ function. However, when we combine *prospero* loss with loss of glutamate receptor subunits, there is a marked drop in larval locomotion and NMJ neurotransmission. On a superficial level, these results suggest impaired homeostasis. Yet closer examinations of the synapse and tissue reveal stark developmental and physiological phenotypes, including impaired NMJ elaboration, shallow nerve/muscle depth, very low input resistance, and a fragile and disorganized musculature. We conclude that under specific environmental or genetic conditions, homeostatic challenges like neurotransmitter receptor loss can prime synapses and target tissues for extreme developmental and functional impairment.

Disclosures: D. Zwiefelhofer: None. **B. Mallik:** None. **K.M. Lembke:** None. **C. Frank:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.02/B6

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R35NS111562

Title: Synaptic and intrinsic homeostatic mechanisms sense distinct aspects of neocortical circuit activity

Authors: *W. WEN[1], G. TURRIGIANO[2];
[1]Biol., [2]Dept of Biol., Brandeis Univ., Waltham, MA

Abstract: To reliably perform computations, neocortical circuits need to maintain network stability via a repertoire of homeostatic plasticity mechanisms that compensate for learning or developmental perturbations. Accumulating evidence shows that several distinct features of network activity are under homeostatic control, and may be independently stabilized by different cellular homeostatic plasticity mechanisms. This modularity requires dexterous adjustment of the timing and placement of various forms of plasticity, yet it remains unclear how this remarkable coordination is achieved. Here, we investigated how neocortical circuits coordinate the induction and expression of synaptic scaling (SS) and intrinsic homeostatic plasticity (IHP), two major forms of homeostatic plasticity that target excitation and intrinsic neuronal excitability, respectively. By combining *in vitro/ex vivo* electrophysiology and genetic/pharmacological manipulations, we first examined how SS and IHP interact during expression, and then attempted to dissociate their induction by perturbing different aspects of network excitability. We found that SS and IHP exhibit similar expression timeline after being set in motion, and that IHP is sensitive to molecular interventions that are known to block SS. By perturbing either spiking or NMDAR-mediated activity in the network via different pharmacological agents, we showed that SS and IHP are independently induced by sensing reduced spiking and diminished NMDAR signaling, respectively. Thus, we asked whether experience-dependent manipulations that alter NMDAR-dependent activity with little impact on mean firing rate can selectively recruit IHP without engaging SS *in vivo*. Measurements of intrinsic excitability and synaptic strength across light/dark transitions revealed that light increases correlated activity and downregulates intrinsic excitability, while synaptic strength is unchanged. We further demonstrated that the light-driven decrease in intrinsic excitability is sensitive to acute suppression of NMDAR activity, suggesting that light-driven correlated firing induces IHP by enhancing the activation of NMDAR. Our data provide evidence that SS and IHP are driven by different activity sensors and are thus sensitive to distinct aspects of circuit activity, yet rely on similar signaling pathways during expression. These results are consistent with a modular model where SS and IHP are independently recruited to serve the homeostasis of distinct network functions.

Disclosures: W. Wen: None. **G. Turrigiano:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.03/B7

Topic: B.05. Synaptic Plasticity

Support: IISER Pune Fellowship
Pratiksha Trust Extra-Mural Support for Transformational Aging Brain Research(EMSTAR/22/078)

Title: Astrocytes modulate operating point of long-term plasticity induction in hippocampal synapses

Authors: *S. SHROTRI, S. NADKARNI;
IISER Pune, Pune, India

Abstract: Astrocytes play multiple roles in maintaining and supporting neuronal function. Like neurons, astrocytes release gliotransmitters such as glutamate, GABA, D-serine, and ATP using multiple release mechanisms. The proximity of astrocytic processes to the synapses of the hippocampus gives them a distinct physical advantage for modulating synaptic transmission and plasticity. However, the extent of astrocytic influence is under contention due to the slower release of gliotransmitters as compared to neurons. This sluggishness of release may be rate limiting in their ability to affect activity in normal conditions. To quantify the exact nature of the influence of astrocytes on synapses of the hippocampus, we model activity-triggered vesicular release of glutamate by astrocytes in CA3-CA1 synapses to assess how it influences plasticity. Our model implements two distinct N-methyl-D-aspartic acid (NMDA) receptors – ones containing NMDA subunit 2A (NMDA-2A) and ones containing NMDA subunit 2B (NMDA-2B). The NMDA-2B are located extrasynaptically and are preferentially activated by astrocyte-derived glutamate. Compared to NMDA-2A receptors, the main target of neuronal release, the NMDA-2B receptors show a prolonged calcium influx. The slow closing of these receptors partially compensates for the low release rates of astrocytic glutamate. We simulated a wide range of protocols that initiate synaptic plasticity in hippocampal synapses. Our results show that activation of NMDA-2B by astrocyte-derived glutamate makes the synapses more pliable in that it becomes easier to initiate LTP. We also find that the size of the spine is an important determinant of the extent of astrocyte influence. Astrocyte activity allows for a greater shift in the activity threshold for long-term potentiation of larger spines than smaller ones. When we include the expression of NMDA-2B on the presynaptic terminal of the CA3 neuron in our model, we see that astrocytic release modulates short-term plasticity by affecting the release rate of neurotransmitters. We next investigate synaptic plasticity at distant synapses is affected by local activity at a tripartite synapse. We conclude that astrocytes modulate both short-term and long-term plasticity and may trigger heterosynaptic plasticity in glutamatergic synapses of the hippocampus.

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Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.04/B8

Topic: B.05. Synaptic Plasticity

Support: 1R01MH130428

Title: Presynaptic Epac2 in synaptic potentiation of mossy fiber synapses

Authors: *M. CHIESA[1], D. J. IXMATLAHUA RIBERA[1], J. XU[1], Y.-Z. WANG[2], K. GEBIS[2], J. N. ARMSTRONG[1], J. N. SAVAS[2], A. CONTRACTOR[1,3,4];
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Abstract: Hippocampal mossy fiber (MF) synapses play a key role in the processing of spatial information in the CA3 region of the hippocampus. Functional modifications of MF synapses have been proposed to contribute to cognitive processes that differentiate novel patterns in the environment by affecting the activity of downstream CA3 neurons; a process termed pattern separation. Long-term potentiation (LTP), one of the major cellular forms of MF synaptic plasticity, is mediated by presynaptic cyclic adenosine monophosphate (cAMP) and its downstream effectors. Both protein kinase A (PKA) and exchange protein activated by cAMP (Epac2) have been proposed as presynaptic effectors of MF LTP. In particular, the role of Epac2 in presynaptic plasticity has only recently been demonstrated at MF and other synapses but the mechanisms of how it mediates changes in release probability remain unknown.
To directly evaluate the role of presynaptic Epac2 in regulating MF synapses, we created conditional knockout (cKO) mice in which Epac2 is ablated from granule neurons in the dentate gyrus. Short-term plasticity (STP) of MF synapses was not affected by Epac2 presynaptic deletion. However, MF LTP induced by high-frequency stimulation was decreased following Epac2 ablation. This was associated with a decrease in the size of the readily releasable pool (RRP) of MF synapses. Therefore, presynaptic activation of Epac2 is necessary to maintain MF LTP and regulates synaptic vesicle dynamics. To better understand the signaling pathways that might complement presynaptic Epac2 at MF synapses we performed a comparative proteomic assessment of MF synapses in the cKO mice. Moreover to determine whether targeted deletion of Epac2 in granule neurons affects behavioral measures of cognition we trained mice in an automated touch screen pattern separation task.
This comprehensive study will further our understanding of the plasticity mechanisms at MF synapses, how they affect hippocampal function, and how they ultimately contribute to cognitive processes such as pattern separation.

Disclosures: M. Chiesa: None. **D.J. Ixmatlahua Ribera:** None. **J. Xu:** None. **Y. Wang:** None. **K. Gebis:** None. **J.N. Armstrong:** None. **J.N. Savas:** None. **A. Contractor:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.05/B9

Topic: B.05. Synaptic Plasticity

Support: 150576

Title: Developmental induction of long-term depression in the hippocampus: using chimeric NMDA receptors to establish domain-specific contingencies of pathological plasticity

Authors: *L. C. MCAULIFFE, A. E. FINDLEY, B. H. SULLIVAN, D. A. GUTEMA, T. C. DUMAS, S. K. VEGA;
Psychology, George Mason Univ., Fairfax, VA

Abstract: Developmental induction of long-term depression in the hippocampus: Using chimeric NMDA receptors to establish domain-specific contingencies of pathological plasticity
Authors L. C. McAuliffe, S. K. Vega, I. R. Woodaman, D. A. Gutema, B. H. Sullivan, T. C. Dumas; Psychology, George Mason Univ., Fairfax, VA
Author Disclosures None.
Abstract Long-term depression (LTD) of excitatory synaptic transmission in the hippocampus occurs as a result of low-frequency activation of synaptic N-methyl-D-aspartate (NMDA) receptors. Normal activation of hippocampal NMDA receptors and induction of LTD is involved in hippocampal circuit refinement during late postnatal development and learning and memory in mature animals, while pathological NMDAR activation may lead to disorders such as depression, autism, schizophrenia, and neurodegenerative diseases such as Alzheimer's. Studies have shown NMDARs can act in both an ionotropic and nonionotropic fashion, such that specific domains of individual NMDAR subunits, GluN2A and GluN2B, might differentially contribute to separate aspects of synaptic plasticity. Additionally, the onset of learning and memory abilities is marked by a switch in dominance of GluN2B to GluN2A during the third postnatal week in mice, which is equivalent to about three years of age in humans. It is hypothesized that this switch, which leads to altered composition of NMDARs, lowers the induction threshold for LTD due to changes in the balance of GluN2A and GluN2B intracellular carboxy terminal signaling domains (CTDs). In order to assess the roles of each GluN2 subunit domain in the induction of LTD throughout development, we recorded electrically evoked synaptic field responses in wild type (WT) mice alongside two transgenic mouse lines expressing chimeric NMDA receptors (CTDs swapped between GluN2A and GluN2B) in the forebrain. A 1 Hz induction stimulus (LFS) was implemented for 15 minutes to induce LTD in chimeric and WT hippocampal slices, and fEPSPs were recorded in area CA1 alongside input-output curves and paired pulse stimulation. Although not enough data have been collected yet to perform comparative statistics, recordings will be analyzed via two-way analysis of variance (ANOVA) evaluating age and genotype effects followed by post-hoc analyses of sex effects. Results of the study will provide a further understanding of the molecular underpinnings of LTD on the level of individual NMDA receptor subunit domains, allowing for more specific pharmacological targets for the treatment of various cognitive, mood, and neurodegenerative disorders.

Disclosures: L.C. McAuliffe: None. **A.E. Findley:** None. **B.H. Sullivan:** None. **D.A. Gutema:** None. **T.C. Dumas:** None. **S.K. Vega:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

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Topic: B.05. Synaptic Plasticity

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National Science Centre (Poland) grant SONATINA 2023/48/C/NZ4/00072
National Science Centre (Poland) grant MINIATURA 2023/07/X/NZ4/00687

Title: Dopamine receptors are involved in GABAergic synaptic plasticity induced onto SST interneurons and pyramidal cells

Authors: *P. BRZDAK, K. LEBIDA, J. W. MOZRZYMAS;
Wroclaw Med. Univ., Wroclaw, Poland

Abstract: Dopamine receptors are known to be involved in many physiological processes including synaptic plasticity, spatial learning and memory. Among them D1-type of dopamine receptors was shown to support long-term potentiation (LTP) and reverse long-term depression of excitatory transmission in the hippocampus (Manahan-Vaughan and Kulla, 2003, Mockett et al., 2007). We also have demonstrated that NMDA-induced LTP strongly depends on the activation of D1/D5 dopamine receptors in stratum oriens area (Brzdąk et al. 2019). Whereas the impact of dopamine system in plasticity mechanisms of excitatory transmission is well known, neuromodulation of plastic changes of GABAergic interneuron-interneuron connections is not well understood. Here to check the role of D1/D5 dopamine receptors in inhibitory synaptic plasticity we applied a chemical protocol, a short exposure to NMDA, which is well known to induce iLTP at GABAergic synapses on pyramidal cells (Marsden et al., 2007) and somatostatin positive (SST) interneurons (Brzdąk et al., 2023). We carried out miniature inhibitory postsynaptic currents (mIPSCs) recordings using patch-clamp technique in hippocampal slices from SST-tdTomato mice and optogenetic experiments in acute slices from PVCre-Ai32 mice. Our results show that exposure to D1-like dopamine receptor antagonist SCH23390 increases the amplitude of mIPSC recorded from SST interneurons while in the presence of its agonist SKF-38393 inhibitory transmission remains unaffected (SCH: relative to baseline: 110±4%, n = 5, SKF: 99 ± 5%, n = 9). Moreover we found that CA1 pyramidal cells and SST interneurons no longer express iLTP following D1-like dopamine receptor antagonist application (SST: 86±3%; n=6; PC: 84±5%; n=7; CTR: 127±4%, n=9, $p < 0.001$). Since pyramidal cells receive inhibitory input from two major types of GABAergic cells: parvalbumin positive (PV) and SST interneurons we asked whether activation of dopamine receptors modulate inhibitory transmission in input specific manners. We demonstrated that activation of D1/D5 dopamine receptors increase the amplitude of light-evoked PV-mediated-inhibitory postsynaptic currents recorded from pyramidal cells (SKF: 122 ± 8%, n = 7, $p < 0.05$). Taken together our results unveil a key role of D1/D5 dopamine receptors in modulation of inhibitory transmission and its plasticity. In summary our data show that dopaminergic system is involved in shaping the GABAergic plasticity in interneuron-specific manner.

Disclosures: P. Brzdak: None. **K. Lebida:** None. **J.W. Mozrzymas:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

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Program #/Poster #: PSTR322.07/B11

Topic: B.05. Synaptic Plasticity

Support: NIH Innovator Award NIH DP2MH136494
Air Force Office of Scientific Research under award numbers FA9550-22-1-0078 and FA9550-23-1-0701
Efellows Program under award No. NSF2127509
EMBRIO Institute, contract #2120200

Title: Focal cooling modulates cortical coding via compartmentalized changes in the electrical structure of L5 pyramidal neurons

Authors: *M. HABIBIMATIN[1], S. XIAO[2], K. JAYANT[2];
[1]Weldon Sch. of Biomed. Engin., Purdue Univ., Lafayette, IN; [2]Weldon Sch. of Biomed. Engin., Purdue Univ., West Lafayette, IN

Abstract: Focal cooling is a neuromodulatory technique that alters neural dynamics and influences behavior. However, the biophysical mechanisms explaining the impact of cooling on cortical circuits are still poorly understood. In this study, we present a biophysically based account of how L5 pyramidal neurons are impacted by focal cooling from a perspective of neural coding and input-output transformations. Using plasticity protocols, somato-dendritic patch clamping, targeted focal cooling, calcium imaging, and two-photon transmitter uncaging as a way of encoding input information streams across the distal apical tuft and basal dendrites, we show that moderate focal cooling with a temperature drop of ~5°C amplifies plasticity in distal apical tuft but not basal dendrites in an N-methyl-D-aspartate (NMDA) and Kv4.2-dependent manner. This triggers a compartmentalized temperature modulation of dendritic excitability in the apical tuft. Given the sensitivity of tuft dendrites to temperature compared to basal dendrites, we show that moderate focal cooling potently modulates top-down integration and somato-dendritic coupling through altering the electrical structure of dendrites across the basal-distal tuft axis, evidenced by increased amplitude of backpropagating action potentials (bAPs) and Ca^{2+} plateau potentials. We then demonstrate a unique biophysical effect wherein although the calcium plateau is amplified by cooling, the rate of recovery of Na^{+} in the apical dendrite is slowed down, ensuring a reduction in axo-somatic output. Critically, our results reveal a previously overlooked effect wherein the Kv4.2 channel's sensitivity to temperature could be differentially regulated across dendritic regions to impact coding.

Disclosures: M. Habibimatin: None. **S. Xiao:** None. **K. Jayant:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.08/B12

Topic: B.05. Synaptic Plasticity

Support: MRC Grant MR/V034111/1

Title: Blockade of large-conductance Ca^{2+}- and voltage-dependent K^+channels rescue synaptic plasticity deficit in a Cacna1c heterozygous animal model.

Authors: P. E. RICHARDSON, J. HALL, *C. M. TIGARET;
NMHII, Sch. of Med., Cardiff Univ., Cardiff, United Kingdom

Abstract: Variants of the *CACNA1C* gene encoding the α1C subunit of $Ca_V1.2$ L-type voltage-gated Ca^{2+} channel ($Ca_V1.2$-L-VGCC) are robustly associated with risk for major psychoses including schizophrenia and bipolar disorder. In particular, risk-associated common *CACNA1C* variants alter $Ca_V1.2$-L-VGCC expression in the brain. *Cacna1c* heterozygous (*Cacna1c*$^{+/-}$) rats expressing ~50% of brain $Ca_V1.2$-L-VGCC have disrupted synaptic potentiation following theta-burst stimulation (TBP-LTP) at hippocampal CA3-CA1 synapses, underpinning a hippocampal-dependent associative learning deficit[1]. However, the mechanism of the TBP-LTP deficit is not fully understood. Functional coupling of L-VGCCs with Ca^{2+}- and voltage-dependent large conductance K^+ (BK) channels control neuronal excitability, whereas Ca^{2+}-sensitive small conductance K^+ (SK) channels regulate synaptic plasticity. CA1 pyramidal neurons from *Cacna1c*$^{+/-}$ rats show attenuated frequency-dependent broadening of somatic action potentials (AP) during burst firing[1], indicating a BK channel gain of function. We hypothesized a mechanistic link between BK channel activity and the TBP-LTP deficit in *Cacna1c*$^{+/-}$ rats. BK channel blockers Paxilline (1 µM) or Iberiotoxin (IbTX, 0.1 µM) rescued TBP-LTP at CA3-CA1 synapses in hippocampal slices from *Cacna1c*$^{+/-}$ rats. In contrast, block of SK channels with apamin (0.1 µM) did not restore TBP-LTP in *Cacna1c*$^{+/-}$ rats. IbTX prolonged the duration of somatic APs in both genotypes and increased the decay time of excitatory post synaptic potentials in *Cacna1c*$^{+/-}$ but not wild-type neurons. These observations indicate that the deficit in synaptic plasticity in *Cacna1c*$^{+/-}$ CA1 pyramidal neurons involves a selective dysregulation of somatic and postsynaptic BK channel function and suggest BK channels as molecular target for phenotype rescue in this animal model.
1. Tigaret, C.M., Lin, TC.E., Morrell, E.R. *et al. Mol Psychiatry* **26**, 1748–1760 (2021). doi:10.1038/s41380-020-01001-0

Disclosures: P.E. Richardson: None. **J. Hall:** None. **C.M. Tigaret:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.09/B13

Topic: B.05. Synaptic Plasticity

Support: Krembil Foundation Fund
Labatt Family Network Fund
CAMH Discovery Fund

Title: Alpha Rhythm Subharmonics Underlie Responsiveness to Theta Burst Stimulation via Induced Calcium Plasticity

Authors: *K. KADAK[1], D. MOMI[4], Z. WANG[5], P. OVEISI[6], S. P. BASTIAENS[2], T. MORSHEDZADEH[7], J. D. GRIFFITHS[3];
[2]Krembil Ctr. for Neuroinformatics, [3]Psychiatry, [1]Univ. of Toronto, Toronto, ON, Canada; [4]camh, Krembil Ctr. for Neuroinformatics - CAMH, Toronto, AE, Canada; [5]Rotman Res. Inst. At Baycrest, Toronto, ON, Canada; [6]Krembil Ctr. for Neuroinformatics, Krembil Ctr. for Neuroinformatics; Univ. of Toronto, Toronto, ON, Canada; [7]Whole-Brain Modelling Group, Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada

Abstract: Repetitive Transcranial Magnetic Stimulation (rTMS) with intermittent theta-burst stimulation (iTBS) has proven efficacious in treating major depression (MDD) by inducing long-term plasticity within brain networks germane to neuropsychiatric disorders. The parameters of iTBS, including pulse frequency, dosage, etc., are understood to influence its induced neurophysiological effects and patients' responses in nonlinear and complex ways. However, plasticity outcomes in both rTMS studies and clinical MDD treatments are highly variable and heterogeneous. The precise neural circuitry that rTMS acts upon and the mechanisms through which functional changes are induced also remain largely unknown and difficult to probe. Of particular importance to understanding both the pathophysiology of MDD and rTMS-induced effects is the oscillatory activity captured by electroencephalography (EEG). Alpha rhythms, which are theorized to arise from time-delayed interactions between cortical and thalamic populations, are a dominant spectral signature in resting-state EEG activity and present a plausible physiological feature for tailoring iTBS. By aligning theta burst frequencies with endogenous alpha rhythms, corticothalamic oscillators are theorized to be modulated with greater efficacy than frequency-agnostic protocols, capturing a potential source of response variance and an avenue for personalizing iTBS treatments. We leverage a large-scale computational model of EEG activity to understand the role of resting-state dynamics, synaptic plasticity, and brain-stimulation interactions on iTBS responsiveness. A 4-population corticothalamic neural mass model composed of excitatory and inhibitory neurons of the cortex and thalamus was used. A physiological description of synaptic weight change was applied wherein post-synaptic calcium concentrations and NMDA receptor conductance rates adaptively mediate plasticity effects. iTBS was scaled across pulses-per-bursts and inter-burst frequency parameters, then assessed for pre-post changes in synaptic weights and resting-state activity. Broadband power was suppressed to varying degrees following iTBS. Most notably, protocols with frequencies closely aligned with the 1st subharmonic of the networks' resting-state alpha maximized responsiveness, implying stimulation-endogenous resonance via optimal calcium induction of inhibitory-afferent connections. The present work provides a powerful computational framework for both

researchers and clinicians to model rTMS-induced plasticity effects and tailor iTBS treatments based on a robust and accessible neurophysiological feature.

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Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.10/B14

Topic: B.05. Synaptic Plasticity

Title: Calcium-activated potassium channel activity in hippocampal synaptosomal membranes is reduced during LTP

Authors: *J. FARLEY;
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Abstract: Long-term potentiation (LTP) of synaptic transmission is a widely-studied form of synaptic plasticity that may mediate some forms of memory. Because potassium ion (K^+) channels in presynaptic terminals contribute to regulation of neurotransmitter release at many synapses and are often targets for modulation by a variety of 2nd-messenger and other signaling molecules, I examined the possibility that their activities might change and contribute to LTP. K^+ channels were incorporated from adult rat brain hippocampal synaptosomal membranes into preformed planar lipid bilayers on the tips of patch-clamp electrodes. As in previous work with cortical synaptosomes (Farley & Rudy, 1991, Farley 2004 *Biophys. J*) several large-conductance (> 50 pS) voltage- and Ca^{2+}-dependent K^+ channel types were routinely observed in synaptosomal membranes prepared from hippocampi of unstimulated (sham-operated) and low-frequency stimulation control animals. Based on their sensitivity to changes in patch-pipette potential and free [Ca^{2+}], channels inserted with their voltage- and Ca^{2+}-sensing side facing the bath. In contrast, little channel activity was observed in membranes prepared from animals ~1 hr following *in vivo* widespread induction of LTP at perforant path - dentate gyrus (pp-dg) synapses. To maximize hippocampal regions affected by LTP-stimulation, stimulating electrodes were positioned at the “bottleneck” of Lomo (*Exp Brain Res* 1971). High-frequency stimulation (HFS) consisted of 8 trains, 30 s apart. Each train consisted of eight 0.4 ms pulses at 400 Hz. Low-frequency stimulation (LFS) entailed 8 trains of 8 pulses at 0.1 Hz. Test stimuli used to activate pp-dg synapses were constant voltage, monophasic, square-wave pulses lasting 0.1 ms, delivered at 0.1 Hz. Changes in synaptic transmission within pp-stimulated animals were measured via extracellular field potentials from dg granule cells. LTP was observed for 30 m in 6 different animals from which synaptosomal membranes were subsequently prepared. LTP (measured as a % increase of baseline spike population amplitude 5 m after HFS) ranged from 178 - 287%; the duration of the potentiated field potential measured 30 m following induction was 131-257% of baseline. Potentiation was not observed in any of the six LFS control animals.

Infrequent channel activity from LTP-stimulated synaptosomes was increased by alkaline phosphatase exposure, as well as by the non-specific Ser/Thr kinase-inhibitor, H-7. These results suggest that a phosphorylation-dependent reduction in Ca^{2+}-activated K^{+} channel activities in presynaptic terminal membranes may contribute to maintained expression of LTP at these synapses.

Disclosures: J. Farley: None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.11/B15

Topic: B.05. Synaptic Plasticity

Support: CIHR PRJ 178372
Bell Let's Talk
Brain Canada

Title: Widefield calcium imaging to investigate and optimize plasticity in prefrontal cortex

Authors: *A. ZOLIS[1], S. VENKATESAN[2], E. K. LAMBE[3];
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Abstract: Long term synaptic plasticity in the adult prefrontal cortex is challenging to examine using conventional whole-cell patch clamp electrophysiology. Protocols optimized in the hippocampus are acknowledged to result in more variable potentiation in brain slices from prefrontal cortex of adult mice. Yet, in the prefrontal cortex in vivo, dendritic calcium spikes arising from NMDA receptor plateau potentials are a robust and cognitively-relevant substrate for long term plasticity. Accordingly, we turned to calcium imaging ex vivo and discovered that wide-field imaging with genetically-encoded calcium indicators can detect plasticity-relevant events at the neural population level in prefrontal brain slices. We therefore developed an all-optical approach to study long-term synaptic plasticity using Thy1-GCaMP6f mice. Here, we measure neuronal population fluorescence in response to stimuli before, during, and after induction paradigms. These experiments employ low frequency test pulses and theta-burst stimulation (TBS) protocols. Calcium imaging allows the quantification of events during induction episodes which predict long-term potentiation (LTP). Initial results suggest that there is a strategic advantage in using calcium signals in this manner to refine preclinical stimulation paradigms. Ongoing work is evaluating pharmacological interventions and modified induction paradigms to improve the reliability of LTP in prefrontal brain slices from adult male and female mice.

Disclosures: A. Zolis: None. **S. Venkatesan:** None. **E.K. Lambe:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.12/B16

Topic: B.05. Synaptic Plasticity

Support: Fellowship 725800 (LAM) from CONAHCyT, México.

Title: Early postnatal blockade of NMDA receptors dysregulates CB1 receptor dependent-synaptic plasticity on the perforant path and synaptic filtering and impairs dentate gyrus-mediated spatial discrimination

Authors: *L. A. MÁRQUEZ[1], E. J. GALVAN[2];
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[2]Farmacobiologia, CINVESTAV SUR, Mexico City, Mexico

Abstract: Hypofunction of NMDA receptors (NMDARs) during early brain development represents a convergence point for the onset and further development of psychiatric disorders, such as schizophrenia. Although the cumulative evidence indicates hippocampal dysregulation in schizophrenia, the integrity of the synaptic transmission and plasticity conveyed by the somatosensorial inputs to the dentate gyrus, the perforant path synapses, has barely been explored in this pathological condition. By using extracellular recordings, we determined a series of synaptic modifications of the lateral and medial perforant paths in male rats postnatally treated with the NMDAR antagonist MK-801 (One subcutaneous injection of 0.2 mg/kg MK-801 or saline solution from postnatal days seven to 11). The synaptic dysregulation here reported suggests decreased cognitive performance in spatial discrimination, for which the dentate gyrus is crucial. We identified modifications in the synaptic properties of the medial and lateral perforant paths to the dentate gyrus synapses in acute slices from MK-801-treated animals. Decreased glutamate release and attenuated synaptic strength precede an impairment in the induction of LTP and cannabinoid 1 receptor (CB1R)-mediated LTD. Surprisingly, by inhibiting the breakdown of 2-arachidonoylglycerol (the endogenous ligand of the CB1R) during low-frequency stimulation, LTD was restored in slices from rats treated with MK-801. Finally, we show for the first time that spatial discrimination, a cognitive ability that depends on dentate gyrus integrity, is impaired in rats exposed to transient blockade of NMDARs during early postnatal development. Descriptive and mechanistic evidence reveals the dysregulation of excitatory transmission and synaptic plasticity from the entorhinal cortex to the dentate gyrus. These findings might explain the cellular dysregulations underlying the altered cognitive processing of similar experiences in the dentate gyrus, as observed in individuals at higher risk of developing schizophrenia.

Disclosures: L.A. Márquez: None. **E.J. Galvan:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.13/B17

Topic: B.05. Synaptic Plasticity

Title: Beta-adrenergic receptor activation modulates behavioral timescale synaptic plasticity by regulating multiple forms of heterosynaptic plasticity.

Authors: *T. O'DELL;
David Geffen Sch. Med. UCLA, Los Angeles, CA

Abstract: The modulatory neurotransmitter norepinephrine, acting through β-adrenergic receptors (β-ARs), has an important role in learning and memory and enhances the induction of Hebbian LTP, a form of synaptic plasticity thought to underlie memory formation[1]. Recent findings indicate, however, that a non-Hebbian form of synaptic plasticity, known as behavioral timescale synaptic plasticity (BTSP), underlies hippocampus-dependent spatial learning[2]. Although the effects of β-AR on Hebbian LTP have been extensively investigated, little is known about how β-AR activation regulates BTSP. Thus, I used extracellular recordings of EPSPs to investigate the effects of the β-AR agonist isoproterenol (ISO) on BTSP in the CA1 region of mouse hippocampal slices maintained in-vitro. BTSP was induced by trains of theta-pulse stimulation (TPS, single pulses of 5 Hz presynaptic fiber stimulation) that induce a complex-spike (CS) burst-dependent form of BTSP LTP[3]. Consistent with previous reports[1], β-AR activation enhanced the induction of homosynaptic LTP by a brief, 5-sec-long train of TPS. β-AR activation also enhanced the ability of different synapses activated by sequential, 5-sec-long trains of TPS to interact in a cooperative fashion and undergo LTP. The facilitation of synaptic cooperativity induced by ISO was, however, highly activity dependent. In the absence of ISO, longer TPS trains of TPS (15 sec duration) induced modest homosynaptic LTP and produced a strong, heterosynaptic facilitation of LTP induction at other synapses activated by a 5 sec train of TPS. Strikingly, when this pattern of TPS was delivered in the presence of ISO the homosynaptic LTP induced by 15 sec of TPS was enhanced and the heterosynaptic facilitation of LTP induction was abolished. Notably, in the presence of ISO 15 sec of TPS induced a strong, CS burst-dependent form of heterosynaptic depression. Thus, β-AR activation not only enhances LTP induction but, by facilitating heterosynaptic depression, also induces potent competitive interactions between synapses that suppresses LTP induction. Together, these findings indicate that β-AR activation fundamentally alters key properties of BTSP by modifying multiple forms of heterosynaptic plasticity. 1. O'Dell et. al., Learn & Mem 22: 461-471, 2015, 2. Bittner et. al., Science 357: 1033-1036, 2017, 3. O'Dell, J Neurosci 42: 2647-2662, 2022

Disclosures: T. O'Dell: None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.14/B18

Topic: B.05. Synaptic Plasticity

Support: NIH Grant 1R15DA049260-01A1

Title: Three days of THC Exposure Abolishes CB1-Dependent LTD in VTA GABA Neurons of Young, but not Adult Mice

Authors: *M. VON GUNTEN[1], S. HOFFMAN[2], J. G. EDWARDS[3];
[2]Neurosci., [1]Brigham Young Univ., Provo, UT; [3]PDBio, Brigham Young Univ. Neurosci. Grad. Program, Provo, UT

Abstract: Ventral tegmental area (VTA) dopamine (DA) signaling plays a key role in reward learning and drug dependence. VTA DA cells are tonically inhibited by local GABA interneurons to regulate reward prediction. We previously identified a cannabinoid type 1 receptor (CB1R)-dependent form of long-term depression (LTD) at the excitatory synapses onto these VTA GABA cells which is induced *ex vivo* via high frequency stimulation (HFS). This LTD is dependent on metabotropic glutamate receptor 5 (mGluR5) activation and 2-acylgylcerol (2-AG) production and is developmentally maintained and present in adult as well as adolescent mice. Because adolescents are more susceptible than adults to the cognitive and addictive effects of THC, we sought to understand if age-dependent differences in VTA GABA cell plasticity could be used as an assay system to examine the impact of THC exposure. Therefore, we examined the impact of THC on plasticity in adults versus adolescents using *ex vivo* whole cell electrophysiology with extracellular stimulating electrodes after *in vivo* THC exposure. Following chronic (7-10 days) Δ9-tetrahydrocannabinol (THC) injections, LTD cannot be induced in young or adult mice, while a single day of THC exposure does not affect LTD in young or adult mice. To build off of these findings, we sought to determine if the number of *in vivo* THC exposures required to eliminate LTD is affected by age. Thus, we treated young and adult mice with THC for only 3 days, after which we attempted to induce LTD *ex vivo*. We discovered that LTD is eliminated after 3 days of THC exposure in young mice ($n = 10$, $p = 0.107$), but it continues to be present in adult mice ($n = 6$, $p < 0.001$). This is the first time that age dependent differences in drug-induced plasticity in the VTA have been identified. To further explore these age-dependent differences, we used quantitative PCR in young and adult mice who had been treated with saline or THC. Interestingly, we noted a significant downregulation in CB1R mRNA expression in young versus adult mice ($n = 6$, $p < 0.05$), which could explain the differences in plasticity between young and old mice. Other PCR targets such as BDNF, and endocannabinoid synthesizing elements are currently being explored. These findings suggest that age-dependent differences in VTA GABA cell plasticity could contribute to the increased vulnerability of adolescents to the negative effects of THC.

Disclosures: M. Von Gunten: None. **S. Hoffman:** None. **J.G. Edwards:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

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Program #/Poster #: PSTR322.15/B19

Topic: B.05. Synaptic Plasticity

Support: Whitehall Foundation Grant

Title: Axonal Plasticity in Fear-Learning

Authors: *T. A. MATOS[1], A. MENDEZ[1], J. TETENMAN[4,5], K. GOOSENS[2], J. L. ABLES[3]; [1]Neurosci. & Psychiatry, [2]Neurosci., [3]Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]; [5]Univ. of Washington St. Louis, St. Louis, MO

Abstract: Background: Fear-learning depends on synaptic changes that lead to lasting modifications at the dendrite and axon. Long-term memory formation depends on local protein translation (LPT) at the synapse, yet, little is known about the role of LPT in presynaptic terminals in learning Presynaptic plasticity in the medial-habenula (MHb) cholinergic axons within the interpeduncular nucleus (IPN) affects the freezing response during fear conditioning. Furthermore, studies that ablated cholinergic projections from the mHb to the IPN led to impairments in fear-learning. We seek to understand how LPT is regulated in-vivo to determine its role in fear-learning, hypothesizing that synaptic plasticity in the mHb-IPN circuit and the associated behavioral expression of fear relies upon stimulus-induced LPT. Methods: We used Translating Ribosomal Affinity Purification (TRAP) to capture RNA transcripts from actively translating ribosomes from cholinergic terminals in the IPN. We microdissected the mHB and IPN from ChAT-NuTRAP mice 1h after cued fear-conditioning or controls and then performed TRAP-sequencing (n=10 mice/group/sex/sample, biological triplicates). Differentially expressed genes among the fear and control groups are validated using RNAscope in a separate cohort (n=5 mice/group/sex). Results:TRAP-sequencing data indicates that there are 26 differentially expressed genes (DEGs) in the fear conditioned mice. FosB, a marker of neuronal activation, is upregulated in fear conditioned mice, indicating robust mHB activation with fear conditioning, as expected. However, most DEGs are downregulated, suggesting that much of the stimulus-induced LTP is already completed 1h after fear conditioning. Interestingly, the effect is seemingly driven by female mice, although further analysis is needed. Conclusions: Our results indicate that fear learning induces rapid LPT in cholinergic terminals within the IPN of ChAT-NuTRAP mice. The majority of DEGs are downregulated, suggesting that the process of translation has largely been completed already Future studies will examine earlier timepoints to capture the full ensemble of transcripts recruited for LTP during learning.

Disclosures: T.A. Matos: None. **A. Mendez:** None. **K. Goosens:** None. **J.L. Ables:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.16/B20

Topic: B.05. Synaptic Plasticity

Support: NIH Grant DA054274

Title: D1- and A2A-mediated long-term potentiation of NMDA transmission in striatal medium spiny neurons

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Abstract: NMDA receptor-mediated depolarization plays a role in driving and maintaining transitions to sustained depolarized up-state from hyperpolarized down-state in medium spiny neurons in the striatum. However, while synaptic plasticity of AMPA receptor-mediated transmission is well-described in these neurons, plasticity of NMDA-receptor mediated transmission has yet to be shown. In the current study, we established a protocol that induces LTP of NMDA transmission that is dependent on D1 dopamine receptors and A2A adenosine receptors. To achieve this, we obtained sagittal brain slices (280 μm) from 3-5 weeks old Sprague-Dawley rats (n=25) and made whole cell recordings at -55 mV from medium spiny neurons (n=28). To induce LTP, 3-s presynaptic simulation (10 stimuli at 33 Hz) was paired with a train of postsynaptic spikes (7 unclamped action potentials at 15 Hz; evoked at the end of 3-s presynaptic stimulation) in the presence of D1 and A2A agonists (SKF 81297 or CGS 21680, 2 μM each) or in control solution. While pharmacologically isolated NMDA EPSCs were gradually potentiated after induction (10 pairings every 30 s) in the presence of agonists (baseline: 55.4±2.9 pA vs post-induction: 81.7±9.7 pA, n=14, p=0.02), there was no significant increase when induction was done in control solution (baseline: 51.2±3.0 pA vs post-induction: 50.9 ±3.9 pA, n=8, p=0.91). Thus, NMDA EPSC amplitude ~30 min after LTP induction normalized to baseline was significantly greater in the presence of agonists (1.52±0.22 in agonists vs 1.00±0.06 in control, p= 0.04). Analysis of paired pulse ratio revealed no significant change (1.44±0.06 vs 1.48±0.05, n=14, p=0.33), suggesting postsynaptic locus of expression. No significant LTP was observed with repeated delivery of presynaptic stimulation alone (baseline: 43.7±5.5 pA vs post-induction: 45.8±1.8 pA, n=3, p=0.76) while postsynaptic spikes alone caused slight LTD (baseline: 58.5±2.3 pA vs post-induction: 46.8±3.7 pA, n=3, p=0.02), indicating that LTP induction in D1/A2A agonists requires pairing of pre- and postsynaptic activity. This form of associative plasticity of NMDA transmission might play a role in dopamine-dependent associative learning mechanisms in the striatum. We have previously shown that D1/A2A agonists enhance metabotropic glutamate receptor-dependent Ca(2+) signaling that acts to augment spike-induced Ca(2+) signals. Potential involvement of this mechanism in LTP induction will be investigated.

Disclosures: A. Caglayan: None. **H. Morikawa:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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Topic: B.05. Synaptic Plasticity

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Italian MUR PRIN 2022YEPFB7
University of Catania Progetto Piaceri

Title: The blockade of Dopamine D3 receptors improves hippocampal synaptic plasticity and memory via post-synaptic mechanisms

Authors: *V. VACANTI[1], M. TROPEA[1], M. MELONE[2], D. D. LI PUMA[3], G. ACETO[3], B. BANDIERA[3], R. TROVATO[1], M. D'ASCENZO[3], F. CONTI[2], C. GRASSI[3], D. PUZZO[1]; [1]Dept. Biomed. and Biotechnological Sci., Univ. of Catania, Catania, Italy; [2]Univ. Politecnica delle Marche, Ancona, Italy; [3]Univ. Cattolica del Sacro Cuore, Rome, Italy

Abstract: Dopamine D3 receptors (D3Rs) are crucial in cognitive functions, especially memory. Although less abundant than D2 receptors, D3Rs exhibit a higher affinity for dopamine and are expressed in the hippocampus, where they modulate excitatory signals, impacting synaptic plasticity. Previous research indicated that D3R pharmacological blockade or genetic deletion improves cognition, but the underlying molecular mechanisms remain poorly understood. This study aimed to investigate the effects of D3R blockade on hippocampal synaptic function. Using electrophysiological, behavioral, biochemical, and imaging approaches, we analyzed wild-type mice treated with the D3 antagonist NGB-2904 and D3 knockout (KO) models. Our findings revealed that D3R blockade enhances hippocampal long-term potentiation (LTP) and memory primarily via a post-synaptic mechanism. NGB-2904 perfusion increased AMPAR-mediated currents, mEPSC amplitude, and basal synaptic transmission (BST) without affecting afferent volley. Moreover, D3R blockade did not modify presynaptic forms of plasticity such as post-tetanic potentiation and paired-pulse facilitation. Thus, electrophysiological data suggested a post-synaptic role for D3Rs. Quantitative electron microscopy further supported these findings, showing higher D3R expression in post-synaptic dendrites compared to axon terminals. Western blot analysis of the same hippocampal slices used for LTP recordings confirmed increased levels of post-synaptic plasticity-related proteins like PSD95, phosphor(p)-GluA1, and p-CREB in NGB-2904-treated wild-type mice and D3-KO models. In conclusion, our functional, structural, and molecular findings clarify the mechanisms through which D3R blockade modulates hippocampal synaptic plasticity, revealing a predominantly post-synaptic pathway.

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Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR322.18/B22

Topic: B.05. Synaptic Plasticity

Support: R15 MH129932-01

Title: Sex differences in endocannabinoid-modulation of hippocampal CA1 dendritic neurotransmission during adolescence

Authors: *V. SMITH[1], K. K. ALVAREZ[2], N. CALHMAN[2], S. SHAHI[2], C. G. REICH[2]; [1]Neurosci., Ramapo Col. of New Jersey, Mahwah, NJ; [2]Ramapo Col. of New Jersey, Mahwah, NJ

Abstract: Work in our lab demonstrated a robust sex difference of rat endocannabinoid signaling at hippocampal dendritic GABAergic synapses. We observed a mixture of constitutive CB1 activity, tonic eCB production and estrogen-mediated eCB production at adolescent female dendritic synapses (Ferraro, 2020). This is consistent with the literature on perisomatic eCB signaling in females. Importantly, these effects are not reported in similar studies of eCB signaling in males. We hypothesize that this sexual divergence across the somatodendritic axis in adolescent hippocampal pyramidal cells translates into differences in eCB-mediated synaptic plasticity. Field excitatory post-synaptic potentials (fEPSPs) were recorded from CA1 in male and female Sprague-Dawley rat (40-55 days old) hippocampal slices. Following a 10 min baseline, two weak (normally non-LTP inducing) stimulations (30 Hz, 0.5 sec and 50 Hz, 0.5 sec) were applied with 25 min between each stimulation. Then, a stronger LTP-inducing stimulation (100 Hz x 2, 0.5 sec apart) was applied and responses were allowed 30 min to recover. For drug-based experiments, slices were pre-incubated (>1 hr.) with the drug, which was bath applied throughout the experiment. All sample sizes were n= 5 or greater, the size needed for 80% statistical power. We observed significant sex differences in LTP induction thresholds. During the 30 Hz stimulation, male slices exhibited ~115% increase in response magnitude, whereas female slices increased ~150% over baseline values. Male slices required the 100 Hz stimulation to reach response magnitudes of 150% over baseline values. In female slices, blocking CB1 receptors with AM251 (3 µM) impaired LTP induction with 30 Hz stimulation. In females inhibiting the synthesis of Anandamide (AEA) via the LEI401 (NAPE-PLD inhibitor, 10 µM) reduced 30 Hz LTP induction (~130% over baseline values). Thus, AEA is partially implicated lower LTP threshold in females. In male slices, enhancing tonic levels of 2-AG via inhibition of MAG-lipase (JZL184, 100 nM) enhanced LTP induction with 30 Hz stimulation to ~140% compared to baseline levels. The CB1-dependent lower LTP thresholds in female slices is consistent with enhanced CB1-mediated suppression of GABAergic neurotransmission, thus resulting in greater excitatory drive in female CA1. Furthermore, the decrease in male LTP threshold via an increase in 2-AG tone suggests a lower excitatory drive in male CA1. Our preliminary data support the hypothesis that sex differences in tonic eCB activity are observed in eCB-mediated synaptic plasticity.

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Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

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Topic: B.05. Synaptic Plasticity

Support: T32GM144876-02
UMBC Startup Fund

Title: Sex-specific mechanisms underlying long-term potentiation at hippocampus-nucleus accumbens shell synapses

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Abstract: The neurobiological basis of many behaviors that are key for survival has been complicated by sex differences in brain function. These disparities extend to reward-related behaviors, where differences in sensitivity to rewarding stimuli and value are prevalent across species, and to neuropsychiatric conditions such as major depressive disorder, where there are well-documented differences in the response to antidepressant treatments. Such differences may stem from distinct reward-related neuronal activity so it is essential to further investigate the neurophysiology of both sexes to gain greater insight into brain function and vulnerability. The hippocampus-nucleus accumbens (Hipp-NAc) pathway is a crucial connection where modulation of neuronal activity mediates reward-related behavior. Our previous work demonstrated that long-term potentiation (LTP) of Hipp-NAc synapses is rewarding, and that mice can establish learned associations between Hipp-NAc LTP and the contextual environment in which LTP occurred. Here, we used whole-cell electrophysiology and pharmacology to investigate sex differences and similarities in the mechanisms underlying Hipp-NAc LTP. We observed similar basal synaptic strengths between males and females and also found that LTP occurs postsynaptically with similar magnitudes in both sexes. Despite these similarities, key sex differences emerged in some of the mechanisms used for LTP as males required NMDA receptors (NMDAR) while females utilized an NMDAR-independent mechanism involving L-type voltage-gated Ca2+ channels and estrogen receptor **α**; (ER**α**;), with an interesting interaction between ER**α**; and postsynaptic calcium influx. We also uncovered several sex-similar features as LTP in both sexes depended on CaMKII activity and occurred independently of dopamine-1 receptor activation. Together, our results showcase sex-specific molecular mechanisms for LTP in an integral reward pathway, emphasizing the importance of considering sex as a variable in mechanistic studies. Further characterization of sex-specific mechanisms underlying plasticity will provide novel perspectives on the neurophysiological basis of behavior, shedding light on the diverse processes that shape behavior and influence susceptibility to psychiatric disorders.

Disclosures: A.E. Copenhaver: None. **T.A. LeGates:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR322.20/B24

Topic: B.05. Synaptic Plasticity

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Title: Suppression of hyperactive GluN2B reverses impaired synaptic plasticity and hippocampus-dependent learning in phenylketonuria (PKU) mice.

Authors: *W. SONG, Y.-S. BAE, M.-H. KIM;
Dept. of Physiol. and Biomed. Sci., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Phenylketonuria (PKU), a genetic disorder characterized by elevated blood phenylalanine levels, is a common cause of intellectual disability. However, how elevated Phe levels impair cognitive function remains unknown. In this study, we demonstrate that submillimolar Phe perturbs synaptic plasticity through the hyperactivation of GluN2B-containing NMDA receptors (NMDARs). L-Phe exhibited dose-dependent bidirectional effects on NMDA-induced currents, but did not affect synaptic NMDAR activity in hippocampal CA1 neurons. The hyperactivation of extrasynaptic GluN2B by L-Phe led to an activity-dependent downregulation of AMPA receptors (AMPARs) during burst or sustained synaptic activity. L-Phe administration decreased neural activity and learning performance, which were mitigated by the pretreatment of mice with GluN2B inhibitors. Furthermore, pharmacological and virus-mediated suppression of GluN2B reversed impaired learning in the PKU model (Pah^{Enu2}) mice. Collectively, these results suggest that the concentration of Phe in the cerebrospinal fluid perturbs extrasynaptic NMDAR function and synaptic plasticity in individuals with PKU, and further suggest that the suppression of GluN2B may be a potential therapeutic strategy to improve cognitive function in patients with PKU.

Disclosures: W. Song: None. **Y. Bae:** None. **M. Kim:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR322.21/B25

Topic: B.05. Synaptic Plasticity

Support: NS080889
R37NS122141

Title: Short-term plasticity at sensory synapses in the adult mouse superficial dorsal horn

Authors: *J. LI[1], M. L. BACCEI[2];
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Abstract: Short-term plasticity (STP) strongly governs the fidelity with which information is transferred across synapses during repetitive activation. Despite significant advances in our understanding of the functional organization of nociceptive circuits within the spinal superficial dorsal horn (SDH), little is known about the degree to which the properties of STP vary across distinct synapses within the SDH network. Here we use *ex vivo* patch-clamp approaches to characterize STP at primary afferent synapses onto spinoparabrachial neurons, inhibitory (VGAT+) interneurons and excitatory (VGAT-) interneurons within laminae I-II of the adult mouse spinal cord. Paired-pulse ratios (PPRs) at A-fiber synapses were similar across all cell types examined, while the PPR of C-fiber synapses onto inhibitory interneurons was significantly lower compared to those onto ascending projection neurons. Similarly, repetitive A-fiber stimulation (20 stimuli at 1-20 Hz) produced frequency-dependent short-term depression (STD) to a similar extent at their synapses onto all three cell types, while the magnitude of STD was significantly greater at C-fiber synapses onto inhibitory interneurons compared to ascending spinoparabrachial neurons. In contrast, we observed no cell type-dependent differences in the rate at which sensory synapses recovered from STD. Interestingly, the bath-application of dopamine (5 μM) failed to significantly modulate the magnitude of STD, or the kinetics of recovery from STD, in any cell type sampled. Overall, the results suggest that, during periods of high-frequency activity, the efficacy of C-fiber synapses onto inhibitory interneurons progressively decreases to a greater degree relative to their synapses onto lamina I projection neurons, which may result in the opening of the spinal “gate” and subsequent increase in the gain of ascending nociceptive transmission to the brain.

Disclosures: J. Li: None. **M.L. Baccei:** None.

Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR322.22/B26

Topic: B.05. Synaptic Plasticity

Support: FWF: DOC 33-B27
FWF: P34696-B

Title: Novel insights into astrocyte-neuron interactions in nociceptive processing at the spinal level

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Abstract: Pathological forms of pain arise from alterations in the processing of nociceptive information within the nociceptive system. The spinal cord holds a pivotal position within this system, and it is understood that changes in synaptic transmission here can be causally linked to the development of pathological pain. Previous studies indicate that astrocytes, beyond their homeostatic functions, also play a significant role in actively regulating synaptic transmission and plasticity in the central nervous system. In this study, we examined whether and how astrocytes influence transmission at nociceptive synapses in the spinal cord, potentially impacting the development of pathological forms of pain. We used Designer Receptor Exclusively Activated by Designer Drugs (DREADDs) to specifically modulate astrocyte activity. Gq-DREADDs or a control construct were delivered to the lumbar spinal cord of male rats using a viral approach, and selectively activated using clozapine-N-oxide (CNO). To evaluate the impact of astrocytic Gq-DREADD activation on synaptic strength, we conducted electrophysiological recordings from identified projection neurons and unidentified neurons in acute spinal slices as well as in deeply anesthetized rats. We discovered that the specific activation of astrocytic Gq-DREADDs led to a de novo, long-lasting depression of synaptic strength (LTD) at spinal C-fibre synapses, both in vitro and in vivo, while having no impact on A-fibre synapses. This newly identified form of LTD was dependent on NMDA receptors and necessitated postsynaptic calcium signalling, yet was independent of postsynaptic G-protein signalling. Additionally, we observed that astrocyte-generated LTD relied on glycine, likely released by glycinergic interneurons in the spinal cord. Here, we demonstrate that the selective activation of spinal astrocytes using Gq-DREADDs triggers LTD at nociceptive synapses. This stands in contrast to the prevailing notion in the literature, which typically suggests that astrocyte activation amplifies pain-related signalling. Our discoveries imply that astrocytes might exert diverse effects on synaptic transmission contingent upon the activating stimulus, thus underscoring their pivotal role in maintaining the equilibrium between inhibition and excitation within nociceptive circuits. Through further experiments, including an examination of the astrocytic secretome, we seek to enhance our comprehension of the dynamic interplay between astrocytes and neurons in the processing of pain.

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Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR322.23/B27

Topic: B.05. Synaptic Plasticity

Support: RGPIN-2022-04162

Title: Inductions of long-term potentiation with biomimetic electromagnetic fields in primary neurons

Authors: *C. E. KANSALA[1], N. ROULEAU[1], N. MURUGAN[1], B. E. MCKAY[2];
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Abstract: Endogenous electromagnetic fields (EMFs) of the brain have received increased attention in recent years as regulators of neural function. However, transcranial magnetic stimulation (TMS) techniques have not yet been developed to accommodate the complex bioelectromagnetic microenvironments of neural tissues that give rise to endogenous EMFs. Given the emerging evidence that phenomena such as ephaptic coupling are integral to cognitive functions including learning and memory, there is a timely need to isolate endogenous brain EMF patterns that may be harnessed for brain stimulation. Previous work investigated how biomimetic EMFs with patterns derived from electrophysiological recordings of long-term potentiation (LTP) could enhance learning and memory in rodents. However, in vitro studies were not performed to determine key parameters underlying its efficacy. Here, we present an in vitro study of LTP inductions using biomimetic EMFs with primary cortical neurons derive from rat embryos and neonates. Isolated primary neurons from E18 or P1-2 Sprague-Dawley rats were cultured in multi-well plates, matured, and later exposed to a low-intensity (~10 μT) LTP-like EMF pattern for 30 mins or 6 hours. We hypothesized that the EMF exposure would activate and amplify markers of synaptic plasticity and LTP in vitro. Our early results suggest increased concentrations of BDNF, elevated expression of immediate early genes, and altered calcium signaling among LTP-EMF-exposed cells relative to sham and other controls. In particular, we compared LTP-patterned EMFs with various sine waves. Immunocytochemistry revealed increased synaptic densities in the LTP-EMF exposed group. This project will reveal if the efficiency of EMF exposure relies on the biomimetic patterning of neuronal firing in discrete brain areas. In addition to furthering an understanding of biomimetic EMFs and their utility as targeted brain activators, the proposed research builds toward engineering non-invasive brain stimulation technologies that recapitulate endogenous brain signaling dynamics for enhanced neurophysiological responses to TMS.

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Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

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Topic: B.05. Synaptic Plasticity

Support: The Canadian Institutes of Health Research (FDN 154292, ENG 173742)
Natural Science and Engineering Research Council of Canada (RGPIN-2020-04176)

Title: Investigating the influence of muscle activation on theta burst transcranial ultrasound stimulation-induced plasticity in the human motor cortex

Authors: *N. NASRKHANI[1], R. CHANG[1], A. BHATTACHARYA[1], R. CHEN[1,2];
[1]Univ. Hlth. Network, Toronto, ON, Canada; [2]Medicine, Univeristy of Toronto, Toronto, ON, Canada

Abstract: Low-intensity transcranial ultrasound stimulation (TUS) is a novel non-invasive brain stimulation (NIBS) method with deeper and more focal penetration compared to other NIBS, like transcranial magnetic stimulation (TMS). The theta burst TUS (tbTUS) protocol increases cortical excitability for 30-60 minutes post-stimulation, inducing long-term potentiation (LTP)-like effects in the primary motor cortex (M1). In LTP-inducing TMS protocols, M1 excitability is influenced by target muscle activation. Specifically, voluntary contraction of the target muscle before intermittent theta burst stimulation (iTBS) reverses its facilitatory effects to inhibitory, while contraction after iTBS enhances its effects. This suggests that LTP-inducing TMS protocols exhibit polarity-reversing metaplasticity, where recently activated neurons become more responsive to new stimulation, while less active neurons become less responsive. However, it is unclear how tbTUS is affected by polarity-reversing metaplasticity. Thus, this study aims to understand how voluntary muscle contractions affect tbTUS-induced plasticity. Based on the results in TMS protocols, we expect pre-tbTUS target muscle contraction will reverse tbTUS-induced facilitatory effects, while post-tbTUS muscle contraction will enhance tbTUS facilitatory effects. The study targeted the right first dorsal interosseous (FDI) muscle hotspot in the left M1. The tbTUS paradigm involved using 80s of sonication with 5Hz bursts. FDI contraction was achieved by index finger abduction for 180s at 20% maximum voluntary contraction. Four interventions were performed in random order on separate days: tbTUS alone, contraction before tbTUS, contraction during tbTUS, contraction after tbTUS. Motor-evoked potential (MEP) amplitude, short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF) were measured using TMS before and at 5, 30, 60, and 90 minutes after the intervention from the FDI, abductor pollicis brevis (APB), and abductor digiti minimi (ADM) muscles. Data was collected from 7 healthy subjects (5 females, mean age 23.7). FDI contraction before tbTUS reduced MEP amplitudes in FDI and APB muscles compared to tbTUS alone. In contrast, contraction after tbTUS increased MEP size at 90 minutes post-stimulation. The changes in MEP amplitude were associated with alterations in intracortical circuits, including increased SICI in pre-tbTUS contraction and increased ICF in post-tbTUS contraction. These results suggest that tbTUS may be subject to polarity-reversing metaplasticity caused by muscle contraction. The study is ongoing, with more subjects being recruited.

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Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

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Topic: B.05. Synaptic Plasticity

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VA RR&D CDA2 RX003790
VA RR&D RX004281-01A2
NIH Grant P20 GM109040

Title: Paired associative stimulation: a tool to assay individual-level sensorimotor plasticity in the lower extremities of individuals in the chronic stage of stroke

Authors: *J. CASH[1], J. H. KINDRED[2], K. HEISE[1], D. E. ARIAS[1], C. M. GREGORY[1], M. G. BOWDEN[3];
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Abstract: A stroke can impair neural communication within sensorimotor pathways thus compromising physical function. Recovery of walking function is mediated by the sensorimotor system's ability to reorganize, i.e., neuroplasticity, to recover function. Paired associative stimulation (PAS) is a potentially useful assay of sensorimotor plasticity that induces facilitation in synaptic efficacy via increases in cortical excitability. PAS can be used in a manner that accounts for individual differences in sensorimotor communication, by modifying the timings of the pairs of stimulation, i.e., peripheral electrical stimulation and transcranial magnetic stimulation (TMS). Considering the heterogeneity in stroke presentation and recovery, PAS may serve as a necessary indicator of lower extremity specific sensorimotor plasticity, however, an individualized faciliatory protocol targeting the lower extremities has never been tested in stroke. The objective of this study was to determine the feasibility of an individualized lower extremity PAS protocol in neurologically healthy individuals and individuals in the chronic stage of stroke (>6 months) to assay sensorimotor plasticity. This study used a pre-post, cross-sectional design. PAS protocols were individualized to account for between-subject variability in sensorimotor signaling by first measuring cortical-level afferent pathways using electroencephalography. Electrical stimulation was applied to the common peroneal nerve to elicit a somatosensory evoked potential (SEP). The SEP latency (at 34ms) was then systematically paired with single TMS pulses to determine the individual-level timing necessary for PAS protocols. Changes in cortically derived responses were characterized by changes in motor-evoked potential amplitude (MEPAmp), elicited by TMS targeting the non-dominant and paretic tibialis anterior muscle, for healthy controls and stroke, respectively. In healthy controls (n=10; 7F/3M; age=43-71yrs) we observed significant increases in the relative change of MEPAmp (median=42.78 [7.31-350.72]%; p=0.0020). In stroke (n=7; 2F/5M; age=62-77yrs) we also observed significant increases in the relative change of MEPAmp (median=97.26 [3.75-129.16]%; p=0.0156). Together, these results demonstrate the feasibility of an individualized PAS protocol as an assay of sensorimotor plasticity targeting the lower extremities. Considering the heterogeneity of stroke presentation, the use and establishment of individualized protocols may benefit our understanding of post-stroke individual-level lower extremity sensorimotor pathways.

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Poster

PSTR322: LTP and LTP: Circuit Plasticity Mechanisms

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Program #/Poster #: PSTR322.26/B30

Topic: B.05. Synaptic Plasticity

Title: Exploring the Subcellular Dynamics of Arc Protein in Neuronal Compartments

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Abstract: The Activity-Regulated Cytoskeleton-Associated (Arc) protein, a key regulator of synaptic plasticity, is distributed across various subcellular locations within the neuron, including dendrites, the soma, and the nucleus. However, the relationship between Arc's functions and its subcellular distributions remains unclear. In this study, we aim to enhance our understanding of Arc's dynamics across these subcellular regions, with a specific focus on the neuronal soma and the nucleus. Our research employs co-immunoprecipitation, expansion microscopy and single particle tracking techniques to elucidate the subcellular distribution of the Arc protein and its dynamics in nucleocytoplasmic transport. Additionally, we have identified interactions between Arc and poly-A-binding proteins (PABPN1 and PABPC1) within both the nucleus and the cytoplasm.

Disclosures: A. Abrahamsen: None. **H. Fevang:** None. **T. Kanhema:** None. **H. Zhang:** None. **C.R. Bramham:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.01/B31

Topic: H.08. Learning and Memory

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Building und Forschung 01GQ0440
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Title: Organization of brain state dynamics by infra-slow field potentials revealed by large-scale graphene active probes

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Abstract: Behavioral and cognitive states change at the temporal scale of minutes and hours, which are orchestrated by slowly changing physiological factors. The infra-slow and ultra-slow components of extracellular field potentials may mirror these transitions across brain regions and states, offering valuable insights into the spontaneous organization of brain dynamics. However, accurately mapping field potentials across extensive areas with high spatio-temporal precision and detecting infra-slow activity reliably has remained elusive. In this study, we employ active graphene neural probes, which allow for DC-coupled recordings with up to 512 multiplexed channels in freely behaving rats. Leveraging this technology, we uncover infra-slow waves linked to state changes related to cortical excitability and arousability. Additionally, we demonstrate that diverse sleep spindle oscillatory patterns are globally modulated by the infra-slow activation of large-scale networks. Our findings show that spatio-temporal patterns of infra-slow field potentials contribute to the spatio-spectral organisation of brain-state dynamics.

Disclosures: R. Garcia Cortadella: A. Employment/Salary (full or part-time):; Ludwig-Maximilians-University, NYU Langone Health.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.02/B32

Topic: F.07. Biological Rhythms and Sleep

Title: Spatiotemporal dynamics of cortical voltage waves during transitions between awake and unconscious brain states

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Abstract: The neocortex exhibits voltage waves and oscillations implicated in sensory processing, attention, memory consolidation, motor control, and various brain disorders. Distinct forms of cortical oscillations are observed in unconscious and awake brain states. Although it is commonly suggested that these different dynamics are influenced by changes in the balance of excitatory and inhibitory neurons and the dynamical stability of cortical activity, the nature of the state transition between awake and unconscious states and the underlying cellular mechanisms remain poorly understood. Traditionally, the brain's voltage oscillations have been monitored electrically at limited spatial resolution. To overcome previous limitations, we performed cell-type-specific fluorescence voltage imaging of oscillations across a 7-mm-diameter glass window implanted above the mouse neocortex of layer 2/3 pyramidal neurons and inhibitory interneurons. We studied the spatiotemporal evolution of neural activity during transitions between wakefulness and an anesthetized state and subsequent periods of recovery from anesthesia. We compared the observed dynamics to the natural slow-wave sleep episodes in a sleep-deprived mouse.
We examined the temporal progression, synchrony, complexity, directionality, and stability of slow-wave and gamma-range voltage activity. By fitting a linear evolution model to the activity patterns, we uncovered stereotypical spatiotemporal modes under ketamine-xylazine anesthesia that were consistent across mice. We investigated the stability of the dominant forms of propagating activity and found that sharp changes in oscillatory frequencies and propagation directions accompanied transitions between awake and anesthetized states. In anesthetized mice, slow-wave cortical oscillations exhibited a characteristic spatial gradient of oscillation frequencies consistent with the direction of activity propagation. In addition to characterizations of spontaneous brain activity, we examined cortical voltage dynamics in response to visual stimuli. Deep anesthesia induced changes in the amplitude and polarity of visually evoked activity, suppressed an oscillatory component of activity and allowed visual responses to spread across a wider anatomic area.
Overall, our study characterizes the spatiotemporal evolution of cortical voltage activity associated with the loss and recovery of consciousness, thereby yielding insights regarding the excitability of cortical neurons and the dynamical transitions of mesoscale cortical brain waves.

Disclosures: V. Kruzhilin: None. **S. Haziza:** None. **R.T. Chrapkiewicz:** None. **Y. Zhang:** None. **M.J. Schnitzer:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.03/B33

Topic: B.07. Network Interactions

Support: Department of Anesthesiology, University of Michigan Medical School, University of Michigan, Ann Arbor, MI
Rackham Predoctoral Fellowship Award, Rackham Graduate School,

University of Michigan, Ann Arbor, MI
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Title: Reversal of propofol or isoflurane anesthesia, with concurrent restoration of functional connectivity, by intravenous administration of the serotonergic psychedelic 2,5-dimethoxy-4-iodoamphetamine

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Abstract: General anesthesia is a pharmacologically induced coma characterized by reduced spatiotemporal complexity and repertoire of brain states. In contrast, the non-ordinary state of consciousness induced by serotonergic psychedelics is associated with increased spatiotemporal complexity and repertoire of brain states. Serotonergic psychedelics, including 2,5-dimethoxy-4-iodoamphetamine (DOI), increase wakefulness, and a previous study showed that intracerebroventricular delivery of DOI reduced the time to passive emergence from isoflurane anesthesia. Based on these previous studies, we hypothesized that intravenous delivery of DOI will produce active emergence from anesthesia (i.e., wakefulness in the continued presence of an anesthetic) and restore electroencephalographic measures typically associated with normal wakefulness. Adult Sprague Dawley rats were surgically prepared to record high-density (30-channel) EEG across the cortex and for intravenous delivery of DOI, propofol, and volinanserin (a 5-HT2A antagonist). Baseline wake EEG was recorded for 20 minutes, after which anesthesia was maintained with propofol (N=21, 10 male; 600-1000 μg/kg/min) or isoflurane (N=14, 5 male; 1.1-1.5%) anesthesia for 40 minutes, at which point DOI (0.5 mg/kg) was delivered as an intravenous bolus while the anesthetic delivery continued. Using the EEG data, non-directional (magnitude-squared coherence) and directional (frontoparietal normalized symbolic transfer entropy-NSTE) measures of functional connectivity were analyzed before and after DOI delivery in rats receiving propofol or isoflurane anesthesia. DOI administration produced signs of wakefulness, including purposeful movements, in 21/21 propofol rats and 14/14 isoflurane rats. Furthermore, DOI-induced wakefulness was accompanied by restoration of coherence and NSTE in the medium (65-115Hz) and high (125-165Hz) gamma bands ($p<0.001$). Pretreatment with volinanserin (25 μg/kg) blocked behavioral and EEG changes induced by DOI. Additionally, intravenous delivery of a non-psychedelic 5-HT2A agonist (lisuride, 0.05 mg/kg) neither reversed propofol anesthesia nor induced any significant changes in gamma functional connectivity. To our knowledge, this is the first report of psychedelic-mediated, 5-HT2A receptor-dependent reversal of general anesthesia and restoration of functional connectivity. These data encourage translational study of serotonergic psychedelics, particularly DOI, as reversal agents for unconsciousness.

Disclosures: E.R. Huels: None. **N. Kolbman:** None. **C.W. Fields:** None. **A.G. Nelson:** None. **T. Liu:** None. **G.A. Mashour:** None. **D. Pal:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.04/B34

Topic: B.07. Network Interactions

Title: Functional role of beta oscillations in physical fatigue

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Abstract: Beta-band oscillations have been associated with a wide range of both cognitive and sensorimotor processes. Regarding the latter, beta oscillations prevail particularly in the absence of movements, whereas performing a contraction causes a drop in their power. In line with these findings, it has been suggested that beta oscillations reflect a 'status-quo', which promotes maintaining the current motor state (Engel & Fries, 2010). While this theory proved reliable explanatory power in several studies, it fails to explain changes in beta-band activity due to the accumulation of physical fatigue. In the current study, we aim to reconcile the functional role of beta oscillations during physical fatigue within the status-quo theory. 24 participants (13 women, age: 24 ± 4, mean ± SD) performed 100 isometric knee extensions against a fixed submaximal resistance (20% of their maximal force) in two conditions (either 10 s or 12 s contractions). Using electroencephalography recordings, we identified two distinct beta-band power dynamics in the motor cortex as fatigue rises: (i) a decrease during contraction ($p = .006$, $BF = 5.55$), thought to reflect the heightened motor cortex activation necessary to cope with the muscle fatigue, (ii) an enhancement at rest (i.e., between contractions) ($p = .002$, $BF = 2.71$), assumed to increasingly promote the resting state. These dynamics were identical for both conditions ($p > .27$, $BF < .45$), which will consequently not be further mentioned. We then conducted Granger Causality analyses, which revealed that these modulations were driven by an increasing signal from the prefrontal cortex ($p = .003$, $BF = 7.95$). Finally, we proposed a simple yet biologically plausible spiking network that reproduces the decreasing beta-band power during contractions when simulating increasing physical fatigue ($p = < .001$, $BF = 1.01\times10^{+6}$), providing a mechanistic explanation for our results. Together, our findings place the physical fatigue paradigm within the status-quo theory, thus shedding light on the functional role of beta oscillations in physical fatigue.

Disclosures: P. Matta: None. **R. Baures:** None. **J. Duclay:** None. **A. Alamia:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.05/B35

Topic: B.07. Network Interactions

Title: Eeg microstates as a biomarker of the resting state neurodynamics in astronauts onboard the international space station

Authors: *K. ARMONAITE[1], L. CONTI[1], P. CROCE[2], L. NARICI[3], M. PIANA[4], S. SOMMARIVA[4], F. ZAPPASODI[5], F. TECCHIO[6];
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Abstract: Missions of low Earth orbit spacecraft as well as future interplanetary explorations rely on the optimal performance of crews. Therefore, gaining a better understanding of the effects of micro-gravity, radiation and other harsh living conditions on astronauts' cognitive productivity and well-being is crucial. With this objective, we analyzed data from the ALTEA (Anomalous Long-Term Effects in Astronauts) experiment on board the International Space Station (ISS), which included EEG recordings from three astronauts in space. In order to gain comprehensive insights into the resting state neuronal electrical activity, we analyzed the microstates of the EEG recordings for each subject and trial, where applicable. Data was pre-processed with standard processing methods, and channels with too high electromagnetic interference or environmental noise were removed. Our findings indicate that microstates in space exhibit lower stability with respect to the ones observed on the ground. Specifically, we derived five principal maps from the space data, which showed shorter duration and greater variance between microstates in total time coverage compared to the standard maps (with $p < 0.01$ and $p < 0.05$ respectively). This apparent instability may be attributed to the highly demanding conditions in space that include the exposition to microgravity, constant air-floating inside the space station, and potential fatigue. The results highlight the importance of obtaining long term data in extreme conditions; exploring improved filtering and computational methods to clean signals; and advocating for further investigation into neural activity in astronauts during space travel. These endeavors are crucial for understanding the potential impact of such conditions on cognitive states both in space and in other highly confined and risky environments, like submarines or Antarctica stations.

Disclosures: K. Armonaite: None. **L. Conti:** None. **P. Croce:** None. **L. Narici:** None. **M. Piana:** None. **S. Sommariva:** None. **F. Zappasodi:** None. **F. Tecchio:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

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Program #/Poster #: PSTR323.06/B36

Topic: B.07. Network Interactions

Support: TKI program (2022-2012377) BRAINinBALANCE
NewTDEC Netherlands Organization for Scientific Research (NWO)
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Title: The ratio of high and low-power states of neuronal oscillations is regulated by E/I balance with implications on bistable perception

Authors: *A.-E. AVRAMIEA[1], A. WESTBROOK[2], R. HARDSTONE[3], H. D. MANSVELDER[4], H. BRUINING[5], K. LINKENKAER-HANSEN[6];
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Abstract: The waxing and waning of neuronal oscillations is characterized by long-range temporal correlations (LRTC) whose strength is determined by the balance between excitatory and inhibitory forces in neuronal networks. Recently, these oscillation dynamics have been shown to alternate between high- and low-power states, with such bistability co-occuring with LRTC. However, a deeper understanding of mechanisms relating LRTC, bistability and E/I balance is missing. Here, we use a computational model of critical oscillations to show that in networks with similar structural E/I ratio, bistability can predict the strength of the opposing excitatory an inhibitory forces, while the ratio of high/low power (HLP) oscillatory states mirrors E/I ratio, reflecting the system's criticality as evidenced by avalanche dynamics. We validated the biomarkers in humans, in resting-state EEG datasets. We found that HLP, but not bistability can consistently discriminate between brain disorders and controls, and between brain states, across multiple resting-state EEG datasets characterized by E/I changes. Importantly, HLP outperforms an established method for inferring E/I ratio from neuronal oscillations, demonstrated by its superior ability to discriminate E/I related changes, both in the model and in resting-state EEG data. To determine the function of bistable oscillations, we analyzed EEG recorded while subjects tracked the number of perceived switches in a bistable visual stimulus. We found that, during resting state, HLP, but not bistability, predicts the number of perceptual switches, with increased high-power states leading to fewer switches. Our study shows that a simple ratio of high/low-power oscillatory states can be used for tracking E/I ratio across disease and healthy state. Importantly, the finding of a strong relationship between high/low-power states and bistable percept switches opens the avenue for the multi-level study of E/I ratio, high/low-power states and brain function in brain disorders.

Disclosures: A. Avramiea: F. Consulting Fees (e.g., advisory boards); Aspect Neuroprofiles BV. **A. Westbrook:** None. **R. Hardstone:** None. **H.D. Mansvelder:** None. **H. Bruining:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aspect Neuroprofiles BV. **K. Linkenkaer-Hansen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aspect Neuroprofiles BV.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.07/B37

Topic: B.07. Network Interactions

Title: Improving the estimation of M/EEG-based connectivity using spatial filters with fine-tuned crosstalk

Authors: *N. KAPRALOV[1,2], A. STUDENOVA[1,3], G. NOLTE[4], S. HAUFE[5,6,7,8], A. VILLRINGER[1,9,10], V. NIKULIN[1];
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Abstract: Phase and amplitude coupling between neural oscillations are considered a proxy of communication between neuronal populations. The coupling strength is often derived from EEG and MEG recordings due to their high temporal resolution. However, the spatial resolution of both modalities is lower compared to fMRI, which makes the interpretation of the results harder. One of the major challenges for the recovery of M/EEG sources and the interpretation of the obtained data is the field spread. To account for this effect, source space analysis is widely used for the estimation of activity in the regions of interest (ROIs) as well as interactions between them. Time courses of activity in ROIs are typically obtained in two steps: (1) inverse modeling followed by (2) aggregation of time courses of activity for source dipoles (later referred to as sources) within the ROI. For both steps, multiple methods exist, and so far there is no clear favorite among them in the literature. Yet, the choice of methods affects the results of the subsequent analyses, for example, when estimating functional connectivity. The discrepancies in results between different methods could be driven by inconsistencies in the spatial origin of the extracted signal. In the current study, we introduce two criteria for assessing the spatial origin of the extracted ROI time series. On one hand, the contribution of sources within the ROI to the extracted signal should be as high as possible compared to sources outside the ROI. On the other hand, the contribution of sources within the ROI should be homogeneous to ensure that activity from the whole ROI is extracted. We use these criteria (referred to as ratio and homogeneity, respectively) to compare existing methods for source space analysis. For both criteria, we develop analytic expressions based on the cross-talk function (CTF), which reflects the contribution of all sources to the extracted signal. In addition, we derive a spatial filter that optimizes a linear combination of the criteria. Through extensive simulations, we show that the CTF ratio reflects the quality of reconstruction of ground truth activity and connectivity, while higher homogeneity leads to improved robustness to unknown ground truth source locations. In addition, we show that the CTF ratio is ROI-specific and gets lower for regions that are further away from the recording sensors. Activity that originates from ROIs with low CTF ratios might be overshadowed by other regions, making the information about genuine connectivity patterns

inaccessible. Introduced criteria and the CTF itself help to visualize the origin of the extracted signal and allow optimizing the extraction of ROI time series.

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Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.08/B38

Topic: B.07. Network Interactions

Support: ANR Grant 21-CE37-0033-02

Title: Repercussion of cTBS-induced cortical excitability changes on phase-amplitude coupling in resting-state EEG

Authors: *A. ER;
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Abstract: Electroencephalography (EEG) is driven by oscillations arising from the synchronized activity of cortical neuronal populations. Phase-amplitude coupling (PAC) refers to the phenomenon in which the amplitude of high frequency oscillations is modulated by the phase of lower frequency oscillations. It has been suggested that the excitation/inhibition (E/I) balance in the brain plays a critical role in the modulation of PAC. However, this has not yet been conclusively proven with human experimental data in the literature. Continuous theta burst stimulation (cTBS) is an inhibitory repetitive transcranial magnetic stimulation (rTMS) protocol that can be used to temporarily disrupt neural activity in humans (Goldsworty et al. 2012). We hypothesized that paired cTBS modifies PAC and our objective was thus to investigate PAC before and after cTBS. Scalp EEG (64 channels, 10-20 montage; 2-kHz sampling rate; 0.03-1330Hz bandwidth) and surface electromyography (EMG; right first dorsal interosseus, FDI; amplified x1000; 2-kHz sampling rate; 10-500-Hz bandwidth) were collected in 10 healthy right-handed controls during resting state with eyes closed before and after paired cTBS over the primary motor cortex (M1; 9-cm round coil; 3 pulses at 50 Hz x 200; 0.7 x resting motor threshold, RMT; twice with 10 minutes interval between each cTBS). EEG PAC (Tort et al. 2010) and motor evoked potentials in FDI (MEPs; 9-cm round coil; 1.2 x RMT) were tested before (2 runs of each) and after paired cTBS (up to 60 minutes). For each recording, MEP amplitude was estimated and EEG times series were preprocessed before computing PAC between theta-alpha/beta-gamma oscillations on 11 channels around the cranial vertex (Fpz, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4 and Oz). As expected, MEP amplitude was depressed 10 min. after cTBS and recovered after 55 min. PAC results were also showing a depression 15 mins after cTBS and a recovery after 45min. Our preliminary results suggests that when the brain cortex excitability is downregulated by cTBS, as assessed by depressed MEPs, PAC is also

modified. Thus, our preliminary data give further support to the hypothesis that PAC depends on E/I cortical balance.

Disclosures: A. Er: None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.09/B39

Topic: H.03. Decision Making

Support: 5K23NS117735

Title: Oscillatory correlates of proactive and reactive control in human anterior cingulate and dorsolateral prefrontal cortex

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Abstract: Human cognition requires the ability to overcome habitual responses in favor of goal-aligned behaviors. The dorsal anterior cingulate cortex (dACC) plays a key role in monitoring conflicts and adjusting cognitive control. Specifically, theta power (~4-8 Hz) in the dACC increases during conflict and control demands. When conflicts arise, the dorsolateral prefrontal cortex (dlPFC) is recruited to allocate attentional resources to resolve them. The dlPFC also activates proactively in anticipation of control-demanding tasks, and reactively adjusts behavioral responses. Furthermore, low-frequency synchrony between the medial and lateral prefrontal cortex regions facilitates processing of errors and conflicts. Traditional studies often utilize scalp electroencephalography (EEG) or functional MRI (fMRI) which struggle with signal localization and timing, respectively. Thus, how dlPFC and dACC contribute to these processes is not well understood. Intracranial EEG (iEEG) provides superior spatiotemporal resolution for localizing fast responses in key prefrontal cortex subregions. Here, we recorded iEEG from 12 surgical epilepsy patients performing a modified Stroop task which varied the relative frequency of conflict trials within blocks. Data were bipolar rereferenced and bandpass filtered 0.5 to 300 Hz before epoching around stimuli (-0.5s to 2s). Response times (RTs) were significantly longer in conflict trials compared to congruent trials. Furthermore, congruent trials preceded by conflict trials exhibited longer RTs than when preceded by congruent trials, demonstrating behavioral adaptation to conflict consistent with greater recruitment of cognitive control resources. We used single-trial linear mixed models (LMMs) to predict oscillatory power in the dlPFC and dACC, which showed significant modulations of high frequency activity (75 - 150 Hz). To examine how prior conflict leads to adaptation, we used LMMs to test whether RTs predicted power in congruent trials following conflict trials (iC). We found reduced theta power with longer

responses early in the trial, suggesting trials with greater RT adjustments required less theta, potentially due to enhanced proactive control leading to more efficient decision-making. These effects were more pronounced in the dlPFC compared to dACC, in line with the notion that dlPFC is responsible for implementing behavioral adaptations. Overall, these results reveal that neural mechanisms in the dlPFC and dACC play crucial roles in the dynamic regulation of cognitive control and conflict resolution, with dlPFC being more involved in adaptation and preparation and dACC more in reacting to conflict.

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Poster

PSTR323: Oscillations and Synchrony: EEG Studies

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Program #/Poster #: PSTR323.10/B40

Topic: B.07. Network Interactions

Support: NIH Grant R01MH126639
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NIH Grant CRCNS2020

Title: Theta burst modulation of the frontoparietal circuit in humans

Authors: *S. PARMIGIANI[1], C. C. CLINE[2], U. HASSAN[3], M. JEDYNAK[4], O. DAVID[5], C. KELLER[1];
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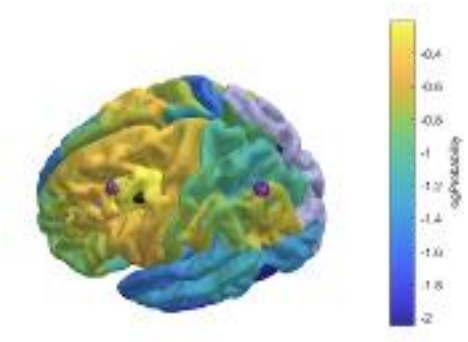
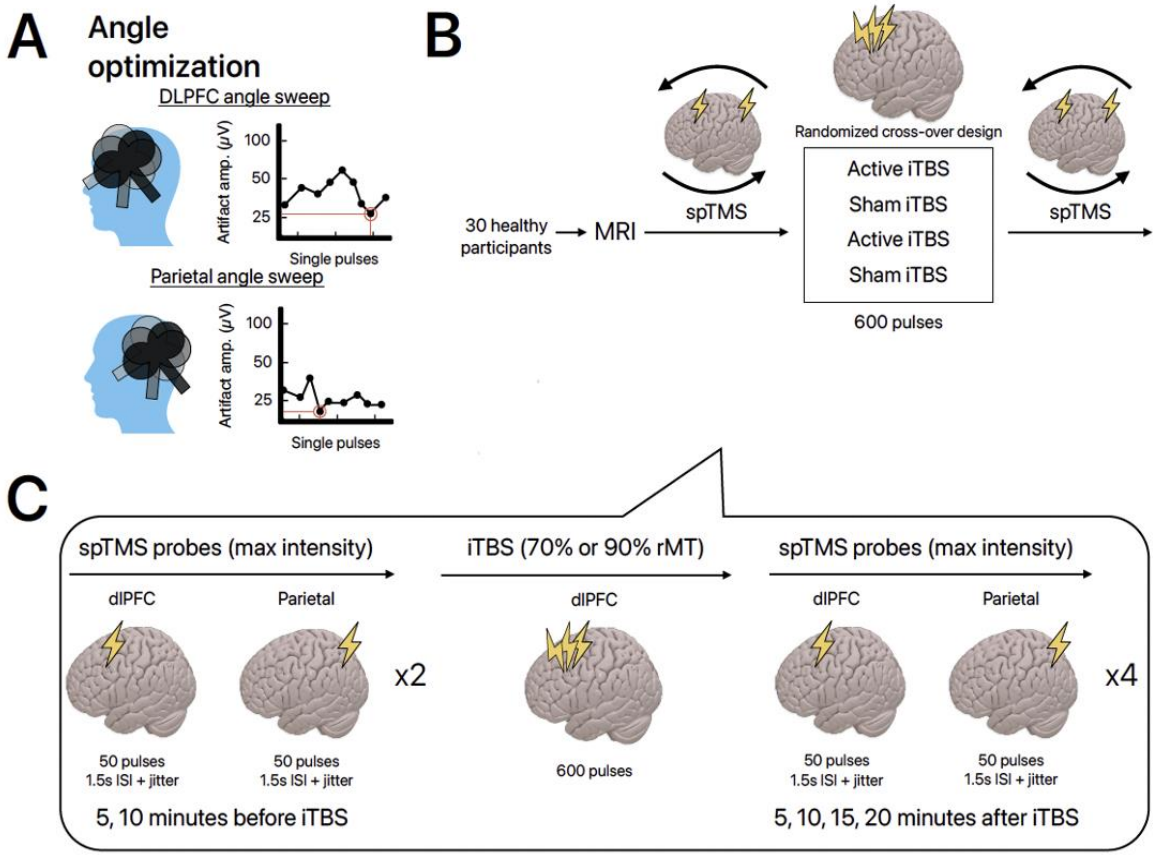
Abstract: Theta burst stimulation (iTBS) is at the forefront for depression treatment, targeting the fronto-parietal central executive network (CEN). The CEN includes the dorsolateral prefrontal cortex (dlPFC), and iTBS over dlPFC improves symptoms. However, whether and to what extent stimulation of the dlPFC modulates the CEN is largely unknown. State of the art iTBS is applied without a detailed understanding of the subregions of the dlPFC that connect to other CEN regions and consideration of individual differences. We used a causal non-invasive circuit interrogation technique (TMS-EEG) to target the portion of the dlPFC connected to the CEN and evaluate the degree of iTBS-induced changes. We first leveraged a large database (F-Tract) of direct brain recordings to localize dlPFC and parietal targets (Fig 1). We applied iTBS and sham-iTBS to 30 healthy controls. We quantified the dlPFC-dlPFC excitability and the dlPFC-parietal inter-connections between nodes of the CEN before, during, and after iTBS (short and long single-pulse TMS assessments over both dlPFC and parietal targets, Fig 2), and contrasted it with sham-iTBS. We explored (1) intra-regional differences in TMS evoked potentials (TEPs), and (2) contrasted them with TEPs collected after sham. Results showed a pattern of changes highly variable between participants, highlighting the importance of

individual localization of treatment targets. This circuit-based individualized approach could pave the way towards a more effective CEN targeting.





Disclosures: S. Parmigiani: None. **C.C. Cline:** None. **U. Hassan:** None. **M. Jedynak:** None. **O. David:** None. **C. Keller:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.11/B41

Topic: B.07. Network Interactions

Title: Neural Mechanisms of Music Listening in Healthy Young Adults

Authors: *L. LINCH[1], C. MARSHALL[1], K. DAVIS[2], M. BRANT[1], E. L. STEGEMOLLER[3]; [1]Neurosci., Iowa State Univ., Ames, IA; [2]Kinesiology, Iowa State Univ., Ames, IA; [3]Neuroscience, Kinesiology, Iowa State Univ., Ames, IA

Abstract: Neuroimaging studies have revealed that listening to music stimulates the ventraltegmental area (VTA), suggesting that music engages the same dopaminergicnetworks that are involved in reinforcement learning and reward (Menon, 2005).In addition to these reward pathways, the VTA also projects to other corticalareas that are not as well characterized within the literature. The dorsal prefrontalcortex (PFC) receives dopaminergic input from the VTA and is involved in motorplanning and cognition. Previous work in animal models that stimulate the VTAthrough optogenetics result in slow wave Delta band (1-4 Hz) oscillations in theprefrontal cortex (Kim et al., 2017). As such, it may be possible that activity in theVTA can be visualized via measurement of upstream projections to the PFC.The current study observes delta oscillations over the PFC as a tool to assesscortical activity associated with music listening. Data from four wirelesselectroencephalographic electrodes (TP9, AF7, AF8, and TP10) on a MUSEheadband was collected to measure upstream cortical activity associated withstimulation of the VTA with preferred music. Percent change scores of corticaloscillations from female healthy young adults (N=8) were assessed duringpreferred music listening and white noise conditions. A paired samples t-test wasconducted to compare the effect of listening conditions on delta oscillations foreach electrode. Effects sizes were obtained using Cohen's d. There were nosignificant differences between listening conditions, $t(7) < 1.11$, $p > 0.31$.However, there was a moderately strong effect size (preferred music mean ± SE= -21.80 ± 8.90; white noise mean ± SE = 7.83 ± 16.27; $d = 0.79$) forcomparisons between music and white noise conditions for electrode AF8 (rightPFC). This suggests that the study is currently underpowered, however, thesepreliminary results support the notion that stimulation of the VTA with preferredmusic may increase delta power over the dorsal PFC. Going forward, additionalparticipants will be collected, and this work will be extended to person’s withParkinson’s disease to better understand the neural mechanisms associated withmusic listening and motor impairment.

Disclosures: L. Linch: None. **C. Marshall:** None. **K. Davis:** None. **M. Brant:** None. **E.L. Stegemoller:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.12/B42

Topic: B.07. Network Interactions

Title: Infraslow EEG activity modulates semantic priming

Authors: C. KELLEY[1], M. SCHIN[1], T. VOLPP[1], ***M. DASH**[2];
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Abstract: Infraslow activity is routinely observed in the electroencephalograph (EEG) as slow voltage fluctuations (<0.1Hz) spontaneously present throughout the brain. A wide range of behaviors and cognitive processes have been shown to be modulated by infraslow activity. The mechanisms underlying such modulation remain unclear, though infraslow fluctuations in attention and/or neuronal excitability appear to be likely candidates. To explore the contributions of these putative mechanisms, we implemented a semantic priming task in which participants' reaction times to target word presentations are influenced by the target word's semantic distance to a previously presented cue word. From 40 participants (aged 18-22, 30 females and 10 males), and throughout 240 word pair presentations to each participant, we continuously recorded neuronal activity via a 32-channel EEG. Consistent with previous research, participants responded significantly quicker ($F(2,72) = 107.80$, $p<0.001$) to semantically-related word pairs (571.43 ± 23.60ms) as compared to unrelated word pairs (604.94 ± 22.34ms) and nonword pairs (774.61 ± 32.79ms). Strikingly, across all cue-target pair types, participants' reaction times were also significantly affected by the instantaneous phase of spontaneous infraslow fluctuations ($F(7,259) = 2.65$, $p<0.05$), an effect that produces comparable differences in reaction time (e.g. mean reaction times at infraslow peak, 678.96 ± 34.67ms, vs. at infraslow trough, 633.29 ± 21.37ms) to those observed between semantically-related and unrelated pairs. To assess whether this infraslow modulation is driven by shifts in attention and/or neuronal excitability we are further analyzing these data to determine whether 1) there is an interaction between infraslow phase and cue-target pair type and 2) whether distinct components of evoked responses (e.g. P100 and N400) previously associated with attention or semantic distance likewise vary across the infraslow phase. In doing so, we can use a well-established behavioral paradigm (semantic priming) and similarly well-established electrophysiological characteristics to separate the relative contributions of changes in attention and/or excitability to behavior associated with spontaneous, infraslow activity.

Disclosures: C. Kelley: None. **M. Schin:** None. **T. Volpp:** None. **M. Dash:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.13/B43

Topic: B.07. Network Interactions

Title: Ripple range High Frequency Oscillations reveal persistent memory-related responses to encoding and free recall of word stimuli.

Authors: *S. PRATHAPAGIRI[1], B. CELIK[3], L. JURKOVICOVA[4], M. KOJAN[5], P. DANIEL[6], P. TABAKOW[7], G. A. WORRELL[8], J. CIMBALNIK[9], M. T. KUCEWICZ[2]; [1]Multimedia systems, [2]Multimedia Systems, Gdansk Univ. of Technol., Gdansk, Poland; [3]Multimedia systems, Gdansk Univ. of technology, Gdnask, Poland; [4]Intl. Clin. Res. Ctr., Brno, Czech Republic; [5]Dept. of Neurol., Brno Epilepsy Ctr., Brno, Czech Republic; [6]Brno Epilepsy Center, Dept. of Neurol. and Neurosurgery, St. Anne's Univ. Hosp. and Med. Fac. of Masaryk University, Brno, Czechia, Brno, Czech Republic; [7]Wroclaw Med. Univ., Wroclaw, Poland; [8]Mayo Clin., Rochester, MN; [9]ICRC, Intl. Clin. Res. Center, St. Anne's Univ. Hospital, Brno, Brno, Czech Republic

Abstract: High-frequency oscillations (HFOs) represent rapid, synchronised bursts of neuronal activity spanning frequencies beyond the conventional gamma bands, offering a potential mechanism for encoding and retrieving specific memory items across widespread cortical networks. HFOs have been widely explored in rodent studies, where they have been associated with cognitive functions during states of wakefulness and sleep. Still, fundamental questions persist regarding the role of this coordinated network activity in human memory processing. In this study, we explored the role of HFOs, especially in the ripple frequency range of 80-200Hz, in the context of a free recall (FR) verbal memory task. Subjects were instructed to memorise a series of 12 words presented sequentially on a computer screen and subsequently recall them in any order following a brief distractor task featuring simple algebraic equations. This task was performed by 20 epilepsy patients implanted with at least 6 sEEG electrode leads for intracranial seizure monitoring. Each participant underwent 15 trials of recalling words from the lists (180 words in total) in one session. We analyzed the intracranial local field potential (LFP) recordings for each word encoding and recall event to elucidate the spatiotemporal dynamics of HFO detections during memory processing compared to control periods of countdown to the trial onset and solving the distractor equations. We first determined electrode channels showing significant HFO responses to encoding and recall of particular words. HFO detections were binned in 10 ms windows and normalized rates were compared across the encoding and the recall phases of the task. Channels that showed elevated rates of HFO detections, which were treated as point processes, were identified at a threshold of mean + 3*std of the average detection rate. We found significant responses to encoding and recall of particular words with evidence of persistent memory related HFO bursting from the moment of word presentation (memory loading) to recall verbalization (memory unloading). Channels exhibiting such persistent HFO bursting were identified across subjects and subsequent experimental sessions in specific brain regions, including the sensory visual and higher-order associational cortex. The specificity of these HFO responses during particular word presentation and preceding its free recall suggests a common neural substrate underlying the formation and retrieval of memory traces. Our results support the neuropsychological theories of neuronal assemblies and provide an electrophysiological substrate to track hypothetical engram activities in the human brain.

Disclosures: S. Prathapagiri: None. **B. Celik:** None. **L. Jurkovicova:** None. **M. Kojan:** None. **P. Daniel:** None. **P. Tabakow:** None. **G.A. Worrell:** None. **J. Cimbalnik:** None. **M.T. Kucewicz:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.14/B44

Topic: B.07. Network Interactions

Support: Center for Psychedelic and Consciousness Research, supported by a gift from the Stephen and Alexandra Cohen Foundation as well as Tim Ferriss, Craig Nerenberg, Blake Mykosky, and Matt Mullenweg

Title: Individual differences in alpha power dynamics across the time course of psilocybin acute effects

Authors: *N. H. HELLER[1], G. LOFLAND[3], F. S. BARRETT[2];
[2]Psychiatry and Behavioral Sci., [1]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Hyperexcitability in the visual cortex is closely associated with reduced power in the alpha bandwidth (8-13Hz) of the EEG power spectrum. Reduced alpha power is also considered the most well-established neurobiomarker of psychedelic drug effects. It has been repeatedly touted as a possible correlate of psychedelic hallucinations (Carhart-Harris et al., 2016; Kometer et al., 2015; Valle et al., 2016). Such claims date back the very first neural measurements made during a psychedelic experience (Chweitzer, Geblewicz, & Liberson, 1937). But how characteristic is reduced alpha power really? Some early studies found the effect reliable (Endo, 1952; Shirahashi, 1960), while others observed the effect in only some participants (Gastaut et al., 1953; Wikler, 1954; Bercel et al., 1956; Brown, 1968). Even in the modern era, one study failed to observe reduced alpha power (Don et al., 1998), though the majority have (Carhart-Harris et al., 2016; Kometer et al., 2015; Muthukumaraswamy et al., 2013; Riba et al., 2002 & 2004; Schenberg et al. 2015; Timmerman et al., 2019 and 2023; Valle et al., 2016). Two sources likely explain these inconsistencies: 1) the time point when alpha power is measured, and 2) individual differences in alpha power modulation. Fluctuations in alpha power are governed by near-critical, state-driven, bistable dynamics, which in turn are governed in part by corticothalamic projections (Freyer et al., 2011); these processes have been implicated in the underlying neurophysiology of psychedelic experiences (Doss et al., 2023; Girn et al., 2023; Vollenweider & Preller, 2020). However, it is unclear how perturbations of these processes evolve across the time course of a psychedelic experience or differ between individuals. Here, we report an exploratory analysis that reveals significant idiosyncratic effects of psilocybin administration on alpha oscillations. In a within-subjects study, EEG data were obtained while participants (8 M, 6 F) rested with their eyes open and closed (2 minutes each) prior to and then 30, 60, 120, 180, 240, and 300 minutes after administration of placebo and 10 mg oral psilocybin. Like other studies, psilocybin significantly reduced alpha power at peak drug effects (120 min; $t(13) = 3.2$, $p < .01$), but only at this time point. Even at peak effect, alpha power increased for two participants. In general, individual subject statistics for alpha power fluctuations, both within rest runs and across time points, reveal significant intersubjective

variation. We present these idiosyncrasies in the context of future attempts to correlate discrete visual hallucinations with dynamic changes in cortical excitability.

Disclosures: N.H. Heller: None. **G. Lofland:** None. **F.S. Barrett:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Wana Brand Foundation. F. Consulting Fees (e.g., advisory boards); Mindstate Design Labs LLC, Gilgamesh Pharmaceuticals, Inc.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.15/B45

Topic: B.07. Network Interactions

Title: Altered signal modulation in bipolar disorder: EEG entropy measures during steady state auditory entrainment

Authors: *W. T. CREEL[1], G. E. DECHANCE[2], C. A. BRENNER[2], R. E. HARTMAN[2]; [1]Loma Linda Univ., Beaumont, CA; [2]Psychology, Loma Linda Univ., Loma Linda, CA

Abstract: Background: Non-linear neural dynamics are increasingly recognized as valuable indicators of brain function and have potential applications in understanding the neural underpinnings of neuropsychiatric diseases. Bipolar disorder (BD) is characterized by impaired entropy modulation when exposed to stimuli and has been proposed as a potential biomarker for the disorder (Molina et al., 2020). Additionally, deviant auditory steady-state responses (aSSR), notably in the gamma range, have been demonstrated across the schizo-bipolar spectrum (Parker et al., 2019). The observed deficits in entropy modulation and aSSR suggest compromised neural adaptability to sensory inputs in individuals with BD. **Method:** The current study examined EEG data from individuals with bipolar disorder (n = 90) and healthy controls (HC; n = 140), obtained during a 40 Hz auditory entrainment paradigm. All individuals with BD were in a euthymic state at the time of data collection. Fuzzy entropy (FuzzEn) analysis was employed to assess whether signal complexity differences occur between BD and HC in response to auditory entrainment. We hypothesized that individuals with BD would exhibit diminished entropy modulation between baseline and stimulus presentation compared to healthy controls, reflecting a less adaptable response to sensory information. **Results:** The results supported our hypothesis with individuals with BD displaying significantly smaller increases in entropy during auditory entrainment compared to HC. Consistent with previous findings (Hernández et al., 2023), our analysis also revealed that individuals with BD exhibit higher entropy levels both at baseline and during auditory entrainment, indicating excessive disorder in neural activity both at rest and while processing sensory information. Finally, entropy increased significantly across the cortex and, notably, in the right hemisphere of the brain compared to the left across all participants during auditory entrainment. This counterintuitive finding, wherein auditory entrainment increased complexity, warrants further investigation into the mechanisms at play. **Conclusions:**

Our findings both reaffirm and expand the understanding of non-linear neural dynamics in individuals with BD, demonstrating impaired neural adaptation to sensory information that may be driven by heightened disorder in brain activity characteristic of individuals with BD. These findings highlight the potential of entropy measures as biomarkers of neural adaptability issues observed in BD.

Disclosures: W.T. Creel: None. **G.E. DeChance:** None. **C.A. Brenner:** None. **R.E. Hartman:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.16/B46

Topic: B.07. Network Interactions

Title: Altered signal modulation in schizophrenia: EEG entropy measures during steady state auditory entrainment

Authors: *G. E. DECHANCE, W. CREEL, R. E. HARTMAN, C. BRENNER; Psychology, Loma Linda Univ., LOMA LINDA, CA

Abstract: Assessments of EEG signal complexity have emerged as promising measures for physiological and psychological states characteristic of numerous psychopathologies (Malihe et a., 2009). Schizophrenia (SZ) has been associated with aberrant sensory processing and a reduced propensity for neural synchronization to auditory steady-state responses at gamma frequencies (30-50 Hz; Cutting et al., 1986; Brenner et al., 2009; Thuné et al., 2016). Additionally, SZ has been linked with deviant neural complexity modulation upon stimulus presentation compared to healthy controls (Xiang et al., 2019). These observations may signify patterns relevant to the diminished sensory adaptability observed in SZ. The current study used fuzzy entropy (FuzzEn) measures of EEG data collected during 40 Hz auditory entrainment from individuals with SZ (n = 86) and healthy controls (HC; n = 140) to investigate entropy modulation during sensory processing in SZ. Stimulus-dependent EEG measures were determined by isolating and averaging the data between stimulus start and end (500ms). Baseline EEG measures were determined by isolating and averaging the 500ms before stimulus presentation. We hypothesized that entropy would decrease upon stimulus presentation in HC, reflecting sensory adaptation. We also hypothesized that persons with SZ would exhibit reduced entropy change between baseline and stimulus presentation compared to HC, commensurate with insufficient sensory acclimation. Results indicated increased entropy between the baseline and stimulus in HC, contrary to our first hypothesis. Additionally, persons with SZ exhibited higher baseline entropy values compared to HC whereas groups did not differ in stimulus-dependent entropy. The SZ group showed a smaller rise in entropy between baseline and stimulus measures than HC, possibly due to elevated baseline entropy. Finally, results demonstrated increased entropy at all electrode sites between baseline and stimulus measures, with the right hemisphere

displaying greater stimulus entropy than the left hemisphere across all participants. These results stress the utility of EEG entropy measures in exploring psychopathology. In line with previous research, these results point to relatively reduced modulations of neural complexity upon stimulus presentation in schizophrenia (Bachiller et al., 2015). Our findings highlight a potential measure for the insufficient sensory adaptability and auditory entrainment observed in schizophrenia, which may be catalyzed by relatively higher baseline neural complexity. The current study may offer further insight into the sensory anomalies characteristic of schizophrenia.

Disclosures: G.E. DeChance: None. **W. Creel:** None. **R.E. Hartman:** None. **C. Brenner:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.17/B47

Topic: F.07. Biological Rhythms and Sleep

Support: R01DC019979

Title: Anterior insula activation, the global signal, and their relation to state-related modulation of auditory processing in human intracranial EEG

Authors: *M. NENTWICH[1], C. CHESEBROUGH[1], N. MARKOWITZ[1], E. FREUND[1], A. D. MEHTA[1,2], S. BICKEL[1,2,3];
[1]The Feinstein Inst. for Med. Res., Manhasset, NY; [2]Departments of Neurology and Neurosurgery, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; [3]Center for Biomedical Imaging and Neuromodulation, Nathan Kline Institute, Orangeburg, NY

Abstract: Brain activity naturally fluctuates between different arousal or attention states. One hypothesis is that the anterior insular cortex (AIC) detects salient events and coordinates switches between states. Other research shows that peaks in the global brain signal are associated with arousal-related brain states. Interestingly, both activity in the AIC and the global signal are known to relate to pupil diameter, a proxy measure for arousal. The relationship between the AIC and the global signal has not yet been investigated in the same subjects using intracranial EEG (iEEG). We hypothesized that activity in the AIC and the global signal should correlate with pupil diameter and reflect states that modulate sensory processing. We also expected activity in the AIC to lead the global signal. We analyzed simultaneous iEEG and pupil tracking data recorded during 30 min of movie watching in 19 patients. We focused on slow fluctuations (<0.25Hz) of the broadband high-frequency activity (BHA, 70-150Hz). We computed the global signal as the average BHA across all gray matter channels. We determined the modulation of sensory processing as phoneme encoding accuracy during moments of high and low activity in the AIC, or the global signal. We found significant peaks in the cross-correlation of the pupil diameter and BHA in the AIC and the global signal, with a delay of 1.1s. Neither activity in the

AIC nor the global signal modulated phoneme encoding. To explore the possibility that the anterior insula coordinates network switches we compute the cross-correlation of BHA in the AIC and all other channels. Inconsistent with our initial hypothesis we found that on average, activity across the brain coincides with the AIC at zero delay. We also found that individual peaks of high activity in the AIC and the global signal rarely overlap (2.5% within a 1s window, N=1091 peaks). Our results have important implications for the proposed role of the anterior insula as a salience detector and switch of attention states. Consistent with previous research, we found a similar relationship of activity in the AIC and the global signal to pupil diameter. In addition, we observed a widespread increase in BHA concurrent with activity in the AIC. Therefore, activity in the AIC might be related to larger global signal fluctuations related to arousal. However, local peaks of BHA in the AIC are distinct from peaks in the global signal, and could reflect the detection of salient internal or external events. Future work will further dissociate differences between the global signal and AIC, in particular by characterizing the modulation of auditory processing at different levels of the cortical hierarchy.

Disclosures: M. Nentwich: None. **C. Chesebrough:** None. **N. Markowitz:** None. **E. Freund:** None. **A.D. Mehta:** None. **S. Bickel:** None.

Poster

PSTR323: Oscillations and Synchrony: EEG Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR323.18/B48

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

Title: Temporal Characterization of EEG slowing Activity Types

Authors: *S. SHARMA;
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Abstract: Life-threatening diseases often remain undetected until irreversible consequences manifest. EEG slowing, a common phenomenon in diseases like epilepsy and dementia, also appears in other critical conditions. In this study, we analyzed data samples from the Temple TUH dataset of EEG slowing to discern distinct characteristics. We hypothesized that we would be able to identify distinct slowing characteristics and patterns with EEG data, identified through various analysis methods. We believe that detection and categorization of these patterns may serve as crucial indicators for the early detection of life-threatening diseases, potentially leading to the development of disease-preventing mechanisms and further insights into disease etiology. We identified characteristics such as generalized or focal slowing and classified them into three categories. Through time-frequency analysis, frequency-domain clustering, time-domain clustering, and additional frequency analysis methods, we explored variations in EEG slowing patterns. Our findings indicate that computational analysis of EEG data is able to identify distinct slowing patterns, suggesting that EEG features could be used for early detection and be pivotal in early intervention and prevention treatment strategies, thus confirming our hypothesis. This

study highlights the critical features of EEG slowing and how these features correlate to specific types of slowing, suggesting a promising path toward new insights into diagnosing and preventing diseases that present with EEG slowing. A comprehensive understanding of the temporal aspects of EEG slowing may lead to further insights into the etiology of these diseases and facilitate future discoveries.

Disclosures: S. Sharma: None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR324.01/B49

Topic: B.09. Glial Mechanisms

Support: NS034007 (E.K.)
NS122316 (E.K.)

Title: Dysregulated translation in neurotoxic reactive astrocytes alters neuronal protein synthesis

Authors: *C. C. SCHULTZ, W. J. LIU, E. KLANN;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Neuronal protein synthesis is essential for forming long-term memories and maintaining synaptic plasticity. Previous research has shown that neurodegeneration is associated with impaired neuronal protein synthesis, indicating that modulation of neuronal protein synthesis is important for maintaining healthy brain function. Although the role of neuronal protein synthesis in synaptic plasticity and memory formation has been widely studied, little is known about the involvement of other cell types, such as astrocytes, in these processes. Support from astrocytes at synapses is key for synaptic plasticity and neuronal function, and our previous work suggests that astrocytes may secrete factors that modulate neuronal protein synthesis. Recently, a specific type of inflammatory astrocyte has been seen to degrade the synaptic function of neurons and ultimately kill neurons. These astrocytes are considered to be neurotoxic, reactive astrocytes, and they are present in diseases associated with neuroinflammation and memory loss. Therefore, we determined whether neurotoxic astrocytes secrete factors that dysregulate neuronal protein synthesis. We collected astrocyte conditioned medium (ACM) from control and reactive astrocytes, then assayed for protein synthesis in neurons treated with this ACM using puromycin, a tRNA analog that is incorporated into a growing polypeptide chain and prematurely terminates translation. We also examined mTORC1 activity by probing for phosphorylated ribosomal protein S6, a downstream effector of mTORC1 signaling. Our preliminary findings suggest that reactive astrocytes exhibit increased translation in comparison to healthy astrocytes, and this increase in translation may be specifically modulated by the mTORC1 pathway. Additionally, neurotoxic reactive astrocytes lead to decreased global protein synthesis in neurons, but they do not alter protein synthesis levels in

HEK cells. This study suggests a relationship between translation in astrocytes and neurons that becomes dysregulated during neurotoxic reactivity, identifying a potential therapeutic target for neurodegenerative disease.

Disclosures: C.C. Schultz: None. **W.J. Liu:** None. **E. Klann:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR324.02/B50

Topic: B.09. Glial Mechanisms

Title: Reactive astrocytes exhibit distinct genomic and transcriptomic states depending on the temporal duration of stimuli

Authors: *E. HILL, C. SOJKA, M. M. SAMPSON, A. KING, S. A. SLOAN;
Human Genet., Emory Univ., Atlanta, GA

Abstract: Astrocytes respond to external or inflammatory stimuli, often produced by traumatic injury, ischemia, or neurological disease. These responses include transcriptomic, morphologic, and functional changes that together comprise a reactive phenotype. While reactive astrocytes can be induced via multiple intrinsic and extrinsic signals, exposure to the microglial-secreted cytokines, TNF- α, Il-1α, and C1q (TIC), is a robust trigger of the reactive state in vitro. However, several important questions remain, including which genomic processes initiate and maintain the reactive state, how the temporal duration of stimuli affects astrocytes, and whether the process is reversible. To explore these questions, we used human cortical organoids (hCO), which recapitulate human cortical development, including the formation of quiescent astrocytes. We validated the reactive astrocyte response by exposing hCOs to TIC for 24 hours and performing bulk and single-cell RNA-seq. We then observed transcriptomic changes reflective of a reactive state. Next, we exposed hCOs to TIC for a time course spanning one day to three months, performing paired ATAC- and RNA-seq at each timepoint. These data reveal the existence of at least two distinct genomic and transcriptomic stages of reactivity — an acute phase (induced by TIC exposure for 1-7 days), and a chronic phase (induced by TIC exposure for 1-3 months). Both stages possess unique differentially accessible transcription factor binding motifs, coupled with distinct differential gene expression profiles, which suggest that the reactive responses in astrocytes are temporally plastic. Analysis of chronic reactive astrocytes also revealed increased genomic accessibility and upregulation of major histocompatibility complex (MHC) class II genes, which encode receptors that are typically only present on professional antigen-presenting cells. We confirmed MHC class II protein expression via immunostaining and fluorescence-activated cell sorting. To investigate reversibility of the reactive state, we allowed hCOs exposed to either acute or chronic TIC to undergo a period of withdrawal. Both acute and chronic reactive astrocytes returned to a quiescent transcriptomic state, implying that the reactive state is highly plastic in the absence of sustained insult. In ongoing experiments, we are now

testing whether MHC class II upregulation in astrocytes promotes an inflammatory state or anti-inflammatory response to cytokine stimulation.

Disclosures: E. Hill: None. **C. Sojka:** None. **M.M. Sampson:** None. **A. King:** None. **S.A. Sloan:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR324.03/B51

Topic: B.09. Glial Mechanisms

Title: Identification of Hub MicroRNAs and Genes Associated with Palmitic Acid-Induced Lipotoxic Stress in Astrocytes

Authors: K. RUIZ[1], **R. KHATRI**[2], A. PINZON[4], S. BONN[3], *M. BREHLER[3], J. GONZALEZ[1];
[1]Exptl. and Computat. Biochem., Pontificia Univ. Javeriana, Bogota, Colombia; [3]Inst. of Med. Systems Biol., [2]Ctr. for Mol. Neurobio. Hamburg (ZMNH), Hamburg, Germany; [4]Univ. Nacional de Colombia, Bogota, Colombia

Abstract: Astrocytes, a crucial component of the central nervous system, play a multifaceted role in maintaining brain homeostasis. However, under conditions of lipotoxic stress, such as elevated levels of free saturated fatty acids like palmitic acid, astrocytes can undergo significant changes in their physiological and biochemical functions. This study employed Weighted Gene Coexpression Network Analysis (WGCNA) to investigate microRNA (miRNA) expression patterns correlated with palmitic acid-induced lipotoxic stress in astrocytes. Our analysis identified hub miRNAs with high Module Membership values, which were then used to predict potential miRNA-target interactions. The overlap of differentially expressed genes (DEGs) from GSE166500 and target genes obtained from in-silico target prediction revealed key genes associated with lipotoxic stress. Association analysis between hub miRNAs and key genes allowed to identify hub genes. This could improve our understanding of the molecular mechanisms underlying neuroinflammation induced by lipotoxic stress. This study aims to uncover potential therapeutic targets for the treatment of neuroinflammation, highlighting the critical role of astrocytes in maintaining brain health.

Disclosures: K. Ruiz: None. **R. Khatri:** None. **A. Pinzon:** None. **S. Bonn:** None. **M. Brehler:** None. **J. Gonzalez:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR324.04/B52

Topic: B.09. Glial Mechanisms

Title: Regulation of neuropathic pain by astrocyte Orai1 calcium channels

Authors: S. TSUJIKAWA[1], ***A. SHETTI**[2], M. NOVAKOVIC[3], M. E. MARTIN[1], M. PRAKRIYA[4];
[1]Northwestern Univ., Chicago, IL; [2]Pharmacol., Northwestern Univ., Chicago, IL; [3]Pharmacol. - Neurosci., Northwestern Univ., Chicago, IL; [4]Pharmacol., Northwestern Univ. - Chicago, Chicago, IL

Abstract: Astrocytes are key regulators of neuroinflammation that underlies the development and maintainance of neuropathic pain. However, the molecular mechanisms underlying astrocytic activation in response to nerve injury are not well understood. Here, we identify the involvement of store-operated Ca^{2+} entry (SOCE) mediated by Orai1 calcium channels in the regulation of astrocytic activation and neuropathic pain. Conditional deletion of Orai1 leads to loss of SOCE in spinal cord astrocytes, indicating that Orai1 plays a dominant role in mediating SOCE in spinal cord astrocytes. SOCE mediated by ATP, a P2-purinoceptor ligand implicated in inflammation-mediated neuropathic pain, was also marked reduced in spinal cord astrocytes. As elevated intracellular Ca^{2+} following SOCE is associated with transcriptional changes, we evaluated the expression of pro-inflammatory and anti-inflammatory cytokines. Gene expression analysis indicated that conditional deletion of Orai1 in spinal astrocytes reduced the expression of numerous pro-inflammatory cytokines including IL-6, TNFα, IL-33 and TGF-β, while the expression of anti-inflammatory cytokines such as IL-10 was unaltered. Furthermore, in vivo studies using a spared nerve injury mouse model and von Frey analysis showed that conditional deletion of Orai1 partially attenuated the development of pain hypersensitivity. However, strikingly mitigation of pain hypersensitivity was observed only in male but not female mice, indicating a sexual dimorphism in Orai1 regulation of neuropathic pain by astrocyte Ca^{2+} signaling. In line with the behavioral phenotype, electrophysioligical analysis of excitatory neurotransmission in the dorsal spinal horn revealed attenuation of central sensitiziation in excitatory neurotransmission in male but not female Orai1 astrocyte KO mice. These findings underscore the significance of Orai1 as a key regulator of astrocytes and neuroinflammation in neuropathic pain. Further studies are required to determine the differential regulation of pain hypersensitivity in male and female mice by astroctye Orai1 channels.

Disclosures: S. Tsujikawa: None. **A. Shetti:** None. **M. Novakovic:** None. **M.E. Martin:** None. **M. Prakriya:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR324.05/B53

Topic: B.09. Glial Mechanisms

Support: NIDA 5P01DA047233
T32DA053558

Title: Astrocytic CREB modulates transcriptomic, neuronal, and behavioral responses to cocaine

Authors: *L. M. HOLT[1], A. M. MINIER-TORIBIO[2], C. J. BROWNE[2], F. MARTINEZ-RIVERA[2], T. MARKOVIC[2], T. M. GYLES[2], E. M. PARISE[2], C. AZIZIAN[2], M. ESTILL[2], E. J. NESTLER[2];
[1]Nash Family Dept. of Neurosci., Mount Sinai Sch. of Med., New York, NY; [2]Nash Family Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Drug addiction is characterized by neurobiological adaptations that support a shift from goal-directed behaviors to habitual, compulsive drug-seeking with persistent effects on cognition and decision-making. To better understand its biological underpinnings, investigations of the transcriptional response to drugs of abuse have demonstrated lasting changes in gene expression throughout the brain's reward circuitry. Historically focused on neurons, emerging evidence increasingly indicates that astrocytes are also involved in disorders of the nervous system, including addiction. However, the astrocyte-specific transcriptome and its regulation following exposure to drugs of abuse have not yet been investigated. We utilized whole cell sorting of astrocytes and RNA-sequencing to characterize the astrocyte transcriptome in the nucleus accumbens (NAc), a key brain region involved in reward-processing, following cocaine self-administration, withdrawal, and "relapse" in mice. We determined that astrocytes exhibit a robust transcriptional response, including context-specific transcriptional signatures. Interestingly, bioinformatic analysis revealed CREB as a highly ranked predicted upstream regulator and CUT&RUN-sequencing identified increased association of CREB bound at DNA in astrocytes following cocaine administration. Viral-mediated manipulation of CREB activity selectively in NAc astrocytes, in combination with a variety of addiction-related behaviors including conditioned place preference and self-administration, reveals that astrocytic CREB increases the rewarding and reinforcing properties of cocaine. This effect is sex-specific, with no change in preference found in females. Finally, preliminary studies indicate that astrocytic CREB modulates neuronal cell type-specific activity to drive cocaine-related behaviors. Together, these data demonstrate that the astrocyte transcriptome responds robustly to cocaine administration and indicates, for the first time, that CREB is a cocaine-induced transcriptional regulator in astrocytes, with implications on neuronal activity and the rewarding properties of cocaine. These findings are particularly interesting, as previously published work demonstrates opposite effects with neuronal CREB in NAc: increased neuronal CREB activity results in cocaine aversion.

Disclosures: L.M. Holt: None. **A.M. Minier-Toribio:** None. **C.J. Browne:** None. **F. Martinez-Rivera:** None. **T. Markovic:** None. **T.M. Gyles:** None. **E.M. Parise:** None. **C. Azizian:** None. **M. Estill:** None. **E.J. Nestler:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR324.06/B54

Topic: B.09. Glial Mechanisms

Support: 3200003935

Title: Potential Fingolimod efficacy in the affective withdrawal phenotype of nicotine use disorder

Authors: *T. ELDER[1], J. R. TURNER[2];
[1]Univ. of Kentucky, Lexington, KY; [2]Univ. of Kentucky, Lexington, KY.

Abstract: Nicotine Use Disorder (NUD) is a major worldwide issue that has had multiple failed treatment plans in the past. NUD causes a high rate of relapse due to the adverse effects of withdrawal phenotypes. This is due to glial cell dysfunction that causes an increase in neuroinflammatory effects within the central nervous system. Targeting glial cells directly, such as astrocytes and microglia, can dampen their activation with a proposed antagonist. A novel drug choice, Fingolimod, could be the answer to these problems. Fingolimod is sphingosine-1-phosphate functional antagonist that is currently on the market and being used for the treatment in Multiple Sclerosis. It has been shown to dampen microglia activation by antagonizing sphingosine-1-phosphate receptors located on astrocytes. This crosstalk between astrocytes and microglia leads to a long-term decrease in glutamate. Fingolimod's target of the ventral hippocampus could potentially have significant efficacy in controlling neuroinflammation.

Disclosures: T. Elder: None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR324.07/B55

Topic: B.09. Glial Mechanisms

Support: Dr. Cliff Feldmann

Title: Using iPSC Derived Astrocytes to Explore Neurotransmitter Homeostasis

Authors: S. J. SZALANSKI[1], **M. ZDROIK**[1], *J. MCGIVERN[2,3];
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[3]Lakeland University, Plymouth, WI

Abstract: Neurotransmitter imbalance in the brain can cause various disease states. For example, Succinic Semialdehyde Dehydrogenase Deficiency (SSADHD) is a rare autosomal recessive disorder that presents itself in early childhood through a wide range of severities. The molecular cause of the disorder is due to a mutation in the metabolic enzyme, succinic semialdehyde dehydrogenase (SSADH), which is essential for the proper catabolism of the neurotransmitter γ-aminobutyric acid (GABA). In the cerebrospinal fluid of patients with SSADHD there is a 2 or greater fold increase in GABA levels and nearly 30-fold increase in gamma-hydroxybutyrate (GHB). Most models have focused on the neuronal aspects of the disease but our focus, using induced pluripotent stem cells, has been to examine the glial contribution. Our previous studies have demonstrated our GFAP+ astrocytes possess the GABA transporter GAT3. This suggests the possibility of an astrocyte contribution in GABA homeostasis in the brain. Here we examine GAT-1 and GAT-3 expression and maturation in the presence and absence of GABA using an updated astrocyte development protocol from induced pluripotent stem cells. We have also explored GABA catabolism in these astrocytes using various methods including ELISA, HPLC, and GCMS. Since GABA is metabolically linked to both glutamine and glutamate, establishing glial culture conditions that can be monitored for neurotransmitter catabolism may be a powerful tool for understanding the influence of glia not only for SSADHD but for a wide range of neurological diseases.

Disclosures: S.J. Szalanski: None. **M. Zdroik:** None. **J. McGivern:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR324.08/B56

Topic: B.09. Glial Mechanisms

Support: University of Virginia Pharmacology Training Grant

Title: The role of cFos+ astrocytes in epilepsy

Authors: *M. J. FAILOR[1], R. P. GAYKEMA[2], A. MACIEJCZUK[1], E. PEREZ-REYES[1]; [1]Pharmacol., Univ. of Virginia, Charlottesville, VA; [2]Pharmacol., Sch. of Med., Charlottesville, VA

Abstract: Motivation: Epilepsy is a neurological condition that millions of people worldwide experience, approximately one third of these patients do not have their seizures adequately controlled under current treatments. Most of the available drugs have a neurocentric mechanism of action. A new approach is needed to discover new targets that can help treatment-resistant individuals. **Methods:** Cell types activated by seizures were identified using the TRAP2 mouse model. Seizures trigger the expression of Cre under the cFos promoter, which is then activated by IP injection of 4-hydroxytamoxifen (4OHT). In mice crossed to the Ai9 tdTomato reporter line, this leads to the expression of tdTomato, “TRAPing” active cells at the time point of 4OHT

administration. Mice were pre-injected with a novel Cre-dependent FLEX2-AAV that delivered a Split Diphtheria Toxin A (SDTA) to cFos+ astrocytes, or a control AAV, both under the control of a GFAP promoter. cFos activation then leads to DTA expression and ablation of the astrocyte. Hybrid kindling, which combines kainic acid and kindling, was used to induce spontaneous seizure development. Mice were implanted with a headset for 24/7 EEG/video monitoring to assess seizure outcome measurements. Immunohistochemistry was performed to examine astrocyte counts, cFos expression, and morphology. **Results:** We discovered that a subset of astrocytes express cFos after a seizure. In contrast to neurons, these astrocytes activate much slower. These cells were more abundant in the CA subfields of the hippocampus, a common seizure focus in this model. We hypothesized that in epilepsy, the cFos genetic program is driving astrocytes into a disease state, and this subgroup of cFos+ astrocytes play either a neurotoxic or neuroprotective role in the development of epilepsy. We found cFos+ astrocytes have distinct morphological differences, with the cells being smaller and having less branching and shorter processes than non-cFos astrocytes. Our pilot study showed that cFos+ astrocytes can be targeted and ablated through AAV delivery of SDTA. We reproduced these results in our EEG experiment, finding that mice given SDTA had significantly less astrocytes in the hippocampus. Importantly, ablation of cFos+ astrocytes led to a significantly higher seizure incidence and frequency. **Conclusion:** cFos+ astrocytes are a newly discovered population that so far has only been studied in mouse models of multiple sclerosis. Our SDTA mice had significantly more seizures than control mice, leading us to believe that cFos+ astrocytes are neuroprotective. Gene therapies could potentially be used to enhance their neuroprotective capabilities to treat epilepsy.

Disclosures: M.J. Failor: None. **R.P. Gaykema:** None. **A. Maciejczuk:** None. **E. Perez-Reyes:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR324.09/B57

Topic: B.09. Glial Mechanisms

Title: Modulation of Epileptic Seizure Progression by Astrocytic GluN2C-Containing NMDA Receptor

Authors: *G. SHELKAR[1], S. DRAVID[2];
[1]Psychiatry and Behavioral Sci., Texas A&M Univ., Bryan, TX; [2]Psychiatry and Behavioral Sci., Texas A&M, Omaha, NE

Abstract: Abstract: Epilepsy is characterized by recurrent seizures due to abnormal neuronal activity. While current treatments target neuronal mechanisms, about one-third of patients do not respond to medications. This highlights the need for an in-depth understanding of the disease's mechanisms to develop more effective therapies. Recent studies have identified a crucial role for

non-neuronal cells, such as astrocytes, in the pathophysiology of epilepsy. Astrocytes express various cell surface receptors, including GluN2C-containing NMDA receptors, but their role in epilepsy is unknown. Our research investigates the impact of astrocytic GluN2C-containing NMDA receptors in PTZ-induced seizures. We discovered that cortical astrocytes exhibit NMDAR currents, which are reduced by GluN2C/2D and GluN2A selective antagonists, suggesting these receptors are composed of triheteromeric GluN1/GluN2A/GluN2C subunits. Additionally, we found that both global GluN2C knockout (KO) mice and those with conditional astrocytic NMDA receptor ablation (AldhGluN1 KO) are more sensitive to PTZ-induced seizures, as demonstrated by significantly shorter latency for seizure generation and increased seizure duration as compared to the respective wild-type (WT) mice, which suggests an increased vulnerability to convulsive seizures. We further assessed the epileptic-like responses in AldhGluN1 KO mice through electrocorticography (ECoG) recordings. We observed that these mice exhibited a significant increase in ECoG power, a hallmark of epilepsy, following PTZ injection compared to the WT mice. Additionally, we explored in vivo effects of AICP, a GluN2C super-agonist. Intracerebroventricular administration of AICP significantly increased seizure latency, decreased seizure duration, enhanced post-seizure recovery, and decreased ECoG power in WT mice compared to vehicle treatment, underscoring its potential therapeutic benefits. These findings collectively suggest that the absence of astrocytic GluN2C-containing NMDA receptors increases seizure susceptibility, illuminating a crucial role for these receptors in modulating seizure activity and offering a novel target for therapeutic intervention.

Disclosures: G. Shelkar: None. **S. Dravid:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

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Topic: B.09. Glial Mechanisms

Support: NIH grant R01MH085802
Simons Foundation Autism Research Initiative (SFARI)

Title: Impaired astrocytic function in Rett syndrome and a potential role of the insulin-like growth factor signaling pathway

Authors: *P. OJHA[1], A. BARLOWE[2], V. KOZAREVA[1], F. SCHULTE[3], D. TOMASELLO[4], Y. OSAKO[1], J. THEILHABER[5], E. FRAENKEL[1], R. JAENISCH[3], M. SUR[6];
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Abstract: Rett Syndrome (RTT) is a devastating neurodevelopmental disorder that affects 1 in 10,000 females. It is caused by mutations in the X-linked gene methyl-CpG binding protein 2 (MECP2), which is present in both neuronal and non-neuronal cells in the brain. Loss of MeCP2 in astrocytes, the most abundant non-neuronal cell type in the brain, leads to morphological impairments in the dendritic processes of neuronal cells and a range of phenotypes, whereas re-expression of the protein in astrocytes substantially rescues phenotypes arising from neuronal loss. These findings suggest that MeCP2 has an important role in astrocytes, which are in turn crucial for regulating neuronal function in RTT. However, the mechanisms by which MeCP2 exerts its function in astrocytes remains unknown. To address this question, we used primary astrocyte-neuron cultures from WT and MeCP2 KO mice and carried out proteomics and transcriptomics analyses of astrocytes as well as a full proteome analysis of the Rett astrocyte-conditioned media (ACM). Synaptogenic proteins that were dysregulated in RTT ACM included SPARC and SPARC-like protein 1. Mutant astrocytes showed a significant suppression of mitochondrial function and cellular respiration related proteins. Importantly, both mutant astrocytes and Rett ACM revealed an upregulation of insulin-like growth factor binding proteins (IGFBPs) that are known to sequester insulin-like growth factor-1 (IGF-1) and affect IGF-1 signaling, with IGFBP2 being the most upregulated. We confirmed the upregulation of IGFBPs by western blots and quantitative real-time PCR. We asked whether the recent FDA-approved drug for treatment of Rett syndrome, a modified N-terminal peptide of IGF-1 [(1-3)IGF-1], targets astrocyte mechanisms. Our proteomics analysis revealed that treatment of cultures with IGF1 peptide led to reversal of expression changes for a substantial number of proteins that were down- or up-regulated in MeCP2 null astrocytes. Activated pathways included those related to mitochondrial function and matrix metalloproteinases. Thus astrocytes contribute importantly to the downregulation of IGF-1 signaling in Rett Syndrome, and are a major substrate for the action of IGF1 peptide in the treatment of the disorder.

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Poster

PSTR324: Astrocytes and Disease Mechanisms

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Topic: B.09. Glial Mechanisms

Support: NIH K00 NS1085
Chan Zuckerberg Initiative

Title: Astrocyte Sema3c in neurodevelopment and Rett Syndrome

Authors: *K. LYON[1], A. PAUMIER[2], A. KANDIKONDA[3], N. J. ALLEN[4];
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Abstract: Astrocytes play a critical role in neurodevelopment, in part, through the secretion of proteins that regulate the formation and function of stable, mature neuronal connections. Altered synapse formation occurs in neurodevelopmental disorders, including Rett Syndrome where neurons show reductions in dendritic complexity and spine number. Rett Syndrome is an X-linked disorder involving loss-of-function of the Mecp2 gene resulting in regressive motor, visual, and cognitive deficits. While Rett Syndrome research has historically focused on neurons, astrocytes are an emerging player. Previous research has shown co-culture of wildtype neurons with Rett Syndrome astrocytes stunts dendritic growth whereas astrocyte-specific restoration of Mecp2 expression in Mecp2-null mice rescues deficits in dendrite morphology and animal behavior, thus indicating a non-cell autonomous effect of astrocytes in Rett Syndrome pathology. Towards identifying key astrocyte secreted proteins involved in neurodevelopment, we previously used unbiased proteomics to identify proteins with altered astrocytic secretion across mouse models of Rett, Fragile X, and Down Syndrome. Included among the identified upregulated proteins is Sema3c, a member of the Class 3 semaphorin family of secreted factors implicated in nervous system development including neurite outgrowth and synapse formation, elimination, and maintenance. Yet, how increased astrocyte Sema3c impacts typical neurodevelopment and if upregulated Sema3c contributes to Rett Syndrome phenotypes is unknown. Given dysregulation across three neurodevelopmental disorders, we explore the hypothesis that increased astrocyte Sema3c is deleterious to typical neurodevelopment and that Rett Syndrome deficits arise, in part, through increased astrocyte secretion of Sema3c. We find that increasing Sema3c protein level in astrocyte conditioned media reduces neurite outgrowth in cultured cortical neurons, showing an inhibitory effect. Additionally, we developed a mouse model to specifically reduce Sema3c in astrocytes of Mecp2 mutant mice and are testing behavioral, histological, and electrophysiological outcomes. Understanding the role of astrocyte secreted proteins in normal neurodevelopment, and in the context of Rett Syndrome, may identify novel avenues for therapeutic targets in neurodevelopmental disorders while also informing on fundamental molecular mechanisms underlying brain function.

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Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR324.12/B60

Topic: B.09. Glial Mechanisms

Title: Effect of metaflammation induced by hypercaloric diet consumption on hippocampal astrocyte population of Wistar rat

Authors: *G. GONZÁLEZ, A. DIAZ, S. TREVIÑO;
Benemérita Univ. Autónoma de Puebla, Puebla, Mexico

Abstract: Metaflammation is a chronic low-grade inflammation process caused by metabolic factors such as sustained nutrient overflow. Metaflammation can cause severe damage to tissue physiological functions and trigger glial cell activity, increasing inflammatory molecule secretion. Astrocytosis is observed in response to inflammatory stimuli. Reactive astrocytes exhibit detrimental or beneficial effects, depending on their differentiation phenotype, neurotoxic (A1) or neuroprotective (A2). Imbalances in the inflammatory response and glial cell activation have been associated with neuroinflammatory and neurodegenerative diseases, yet astrocyte phenotype due to dysmetabolic processes is not highly studied. Therefore, this study aimed to evaluate the effect of metaflammation on astrocyte subpopulations in the hippocampus of male Wistar rats. Male Wistar rats (n=20, 100g weight) were randomly divided into two groups: a regular diet group (NCD) and a high carbohydrate diet group (HCD), fed for three months. At the end of the experimental time, blood samples were taken to determine the oral glucose tolerance, insulin response, triglycerides, free fatty acids, total cholesterol, HDL, LDL, VLDL, and insulin resistance indices. Additionally, we quantified the hippocampal interleukins IL-1β, IL-6, IL-17, IL-10, IL-4, TNF-α, and TGF-β, and double immunolabeling to identify reactive astrocytes (GFAP), A1 phenotype (C1INH), and A2 phenotype (S100A10). Our results demonstrated that consumption of HCD induces metabolic syndrome, hippocampal metaflammation, and A2 phenotype astrogliosis. In conclusion, in the early stages of metabolic syndrome, the A2 astrocytes provide hippocampal cytoprotection, avoiding neurodegenerative processes.

Disclosures: G. González: None. **A. Diaz:** None. **S. Treviño:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

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NIH-NIMHD G12MD007583

Title: Hyperglycemia induces methylation-mediated regulation of kcnj10, a major risk gene encoding kir4.1 channel expression.

Authors: *J. COLON[1], N. ROSADO[2], A. A. ANGUEIRA-LAUREANO[3], J. NAVEDO[1], M. P. MÉNDEZ-GONZÁLEZ[4], S. N. SKATCHKOV[5], D. RIVERA[6];

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Abstract: Hyperglycemia in diabetes alters the functions of the brain. Astrocytes, one of the most abundant cells in the Central Nervous System (CNS), supports neurons by maintaining extracellular homeostasis based on potassium channels such as the inwardly rectifying potassium channels (Kir) found in glial cells (Kir4.1, Kir6.1). Kir4.1 knockdown and Kir4.1 mutations (EAST/SeSAME syndrome), as well as brain ischemic injury, ALS, and Alzheimer's disease, are characterized by glutamate toxicity, epilepsy, ataxia, seizure, severe hypomyelination and early death. Our studies showed that astrocytes cultured in hyperglycemic conditions have reduced expression and function of Kir4.1 channels, like db/db diabetic mice. Since DNA methylation regulates Kir4.1 expression via DNA Methyltransferase 1 (DNMT1), the robust upregulation of Kir4.1 occurs when DNA methylation of the Kir4.1 gene (KCNJ10) is depressed during early development, and we suggest the opposite can be seen during diabetes. Our main **purpose** was to elucidate the expression of DNMT-1 in astrocytes cultured in hyperglycemic conditions. For this study astrocytes were grown under normal (5mM) and hyperglycemic condition (25mM) for two weeks and then the cells were plated in a 6-well plate and treated cells with DNMT-1 inhibitors 5-Aza and RG-108 for 4 days. **Our results** show an increase in the protein levels of DNMT-1 in astrocytes cultured in hyperglycemic conditions vs control. Additionally, we show (i) a correlation between the increased levels of DNMT-1 and decreased Kir4.1 protein levels in astrocytes cultured in hyperglycemic conditions; (ii) alternatively, in astrocytes treated with 5-Aza and RG108, there is a decrease in DNMT-1 protein levels with an increase in Kir4.1 protein levels. In our future studies, we will be testing the functionality of Kir4.1 in astrocyte glutamate clearance and membrane potential when treated with DNMT-1 inhibitors to have a better understanding of the physiological changes in astrocytes and their Kir4.1 potassium channels. There is an urgency in understanding the metabolic pathway causing a disruption in astrocyte function based on methylation-mediated regulation of the major risk gene to develop new treatments to improve the quality of life in diabetic patients.

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Poster

PSTR324: Astrocytes and Disease Mechanisms

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Program #/Poster #: PSTR324.14/B62

Topic: B.09. Glial Mechanisms

Support: Universidad Nacional de Colombia. HERMES 60437

Title: Establishing the hypoglycemia model in a neonatal Wistar rat to study the effect on GLT-1, GFAP and GS proteins of brain astrocytes

Authors: A. L. TARAZONA-CALLE[1], ***Z. DUENAS**[2];
[1]Univ. Nacional de Colombia, Bogotá, Colombia; [2]Ciencias Fisiológicas. Facultad de Medicina, Univ. Nacional de Colombia, Bogota DC, Colombia

Abstract: The first 24 hours postpartum are critical for all newborns, during which transient hypoglycemia occurs (Adamkin et al. 2015). In 2015, the Pediatric Endocrine Society (PES) published recommendations for neonatal management, including immediate treatment when plasma glucose levels are less than 60 mg/dL. However, other experts have suggested tolerating glucose levels of up to 45 mg/dL in healthy neonates (Lezcano et al., 2021). In fact, it is not clear which is the safe glycemic value, particularly in the neonatal brain (Iklé JM et al. 2021). Research on this autoregulation process has focused on analyzing severe hypoglycemia (Shirahata et al., 2015). However, hypoglycemia is a complex phenomenon to study in newborn humans, so animal models allow for experimental approaches. In the initial phase of this study, we employed a sample of 10 individuals to develop the animal model of moderate neonatal hypoglycemia in Wistar rats P14. individuals were divided into three groups. G-1 comprised four individuals (two females and two males) who received a single dose of insulin Lispro (3 IU/kg) intraperitoneally. For an individual weighing 26 g, the dose was 0.07 IU, resulting in an average decrease in blood glucose of 69%, with levels reaching the lower limits between 23 and 28 mg/dL. For G-2 (N=3), the doses administered were 1.5 IU/kg, 1 IU/kg, and 0.8 IU/kg. These doses resulted in blood glucose levels that were still lower than expected. We calculated the dose based on the subject's weight and administered 0.5 IU/kg to G-3 N=3 (1 female, 2 males). For example, a subject with a weight of 32.3 g would receive a dose of 0.016 IU. By administering a series of four doses of rapid-acting insulin (0.5 IU/kg) at 90-minute intervals (ip), allows for the reproduction of a six-hour episode of moderate hypoglycemia (40-50 mg/dL). This resulted in the second phase of the study on the effect of moderate neonatal hypoglycemia on the immunoreactivity of EAAT-2 (GLT-1 in rodents), GFAP and GS proteins in astrocytes of Wistar P14 rats (Muñoz Valencia et al. 2019). The results permit the study of hypoglycemia with greater precision, a broad-spectrum entity that varies considerably with age. Ongoing experiments are conducting related the effect on GLT-1, GFAP and GS proteins of brain astrocytes.

Disclosures: A.L. Tarazona-Calle: None. **Z. Duenas:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

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Title: Role of hypothalamic astrocytes in the development of diet induced obesity

Authors: *T. B. OUELLETTE, K. M. S. O'CONNELL;
The Jackson Lab., Bar Harbor, ME

Abstract: Astrocytes are increasingly appreciated as cells which play an active role in shaping synaptic function and neuronal output. In cortical circuits, astrocytes have a significant effect on neural oscillatory patterns governing a behavioral output, but the role of astrocytes in modulation of neuronal activity in the hypothalamus and their role in shaping appetitive behavior is poorly understood. Factors like high-fat diet, which impact astrocyte expression and function likely have significant effects on neural circuitry governing food intake and energy expenditure. The goal of this project is to understand if astrocytes are necessary and sufficient for maintenance of food intake and body weight via modulation of AgRP neuronal output in the hypothalamus and whether HFD-induced changes in astrocyte K^+ handling are a causal factor in development of obesity. Astrocytes play a key role in maintenance of synaptic excitability and neuronal output by buffering neurotransmitters and ions like K^+ from the extracellular space around the synapse. The inward rectifier K^+ channel Kir4.1 (gene name *Kcnj10*) is the predominant ion channel in astrocytes. The expression of astrocytic *Kcnj10* has not been studied for its necessity in food intake, nor its context in high fat diet. **I hypothesize that changing astrocyte *Kcnj10* expression in the arcuate nucleus of the hypothalamus is sufficient to modulate AgRP neuronal firing rate, energy expenditure and body weight of mice.** In this study, we are characterizing astrocyte recruitment, morphology, expression, and function in the arcuate nucleus of the hypothalamus (ARH) of mice that are fed a high fat diet.

Disclosures: T.B. Ouellette: None. **K.M.S. O'Connell:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

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Eversight

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Title: Endothelin-1 overexpression elicits cellular elastinopathy and reactive astrocytosis in rat optic nerve head astrocytes

Authors: *C. BETANCOURT SZYMANOWSKA[1], A. K. GHOSH[1], V. R. RAO[1,2], E. B. STUBBS, Jr[1,2], S. KAJA[1,2];
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Abstract: Glaucoma is a progressive optic neuropathy characterized by optic nerve head (ONH) remodeling, damage to the optic nerve, and retinal ganglion cell loss. Optic nerve head astrocytes (ONHA) are the primary glial cell in the ONH. Noxious stimuli trigger reactive astrocytosis (RA), a structural remodeling associated with increased expression of glial fibrillary acidic protein (GFAP), enhanced proliferation and migration, reduced stellation, changes in actin cytoskeleton, and altered secretion of extracellular matrix proteins. RA is an early pathological process in glaucoma, underlying the characteristic ONH remodeling. The objective of this study was to determine the putative role of endothelin-1 (ET-1) in RA. Primary rat ONHA cultures stably overexpressing a human V5-tagged endothelin 1 (EDN1-ONHA) construct, or expressing a FLAG-V5 control (control ONHA) construct, were prepared by lentiviral transduction. Overexpression of EDN1 was confirmed by qPCR and ELISA after selection with 2.0 µg/ml puromycin. EDN1-ONHA expressed increased levels of ET-1, as quantified by ELISA (1.3 pg/mL in EDN1-ONHA *vs*. <0.4 pg/mL in control ONHA). EDN1-ONHA exhibited a less-differentiated morphology, significantly enhanced proliferation rates, and increased GFAP expression, suggestive of RA. Gene expression of elastin biosynthetic pathway intermediates, specifically fibulin 2 (*Fbln2*), fibulin 5 (*Fbln5*), lysyl oxidase like-1 (*Loxl1*) and elastin (*Eln*) was reduced by 24% ($p<0.05$), 63% ($p<0.001$), 29% ($p<0.05$) and 63% ($p<0.01$), respectively. Decreased expression of Loxl1 and Eln was confirmed by immunoblotting, showing a 48% reduction in Loxl1 ($p<0.05$) and a 62% reduction in Eln ($p<0.05$). These gene and protein expression changes are consistent with our previous studies investigating the effects of equibiaxial mechanical strain on RA development in rat ONHA. Gene expression for endothelin receptor A (*Ednra*) was similar between EDN1- and control ONHA ($p=0.84$). By comparison, endothelin receptor B (*Ednrb*) was upregulated 5-fold ($p<0.05$). These findings are consistent with the role of Ednrb functioning in ONHA as a "clearance receptor" for ET-1. Our data describe the induction of RA in primary rat ONHA elicited by overexpression of human ET-1, supporting a pathological role of ET-1 in glaucomatous optic nerve head remodeling. Overexpressing ET-1 decreased Loxl1 levels, which are required for normal elastic fiber formation and stabilization. Loss of elastin during RA may contribute to decreased biomechanical compliance of the optic nerve head during glaucoma. Ongoing research is elucidating the signaling pathways mediating these transcriptional changes.

Disclosures: C. Betancourt Szymanowska: None. **A.K. Ghosh:** None. **V.R. Rao:** None. **E.B. Stubbs:** None. **S. Kaja:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR324.17/B66

Topic: B.09. Glial Mechanisms

Support: The Charles M. Vallee Foundation for Long-COVID Research
The University of Miami Team Science Funding Program
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The University of Miami Miller School of Medicine

Title: Ammonia affects critical genes involved in the regulation of neural function in adult human astrocytes

Authors: *R. RAMAMOORTHY[1], N. ELUMALAI[1], A. M. SANCHEZ[2], H. HUSSAIN[3], A. B. RASHED[1], R. RUIZ-CORDERO[1], P. CHEN[1], A. K. CARDEN[1], M. J. PAIDAS[1], A. R. JAYAKUMAR[1];
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Abstract: Hyperammonemia has been strongly implicated in the pathogenesis of acute hepatic encephalopathy. The mechanisms by which ammonia ultimately exerts its neurotoxicity remain poorly defined. Substantial evidence supports the view that astrocytes represent the principal target of ammonia neurotoxicity since no significant or consistent morphologic changes were identified in neurons or other neural cells. Several factors appear to play essential roles in how ammonia impacts the CNS and astrocytes. These include oxidative stress, the mitochondrial permeability transition, mitogen-activated protein kinases, the nuclear factor-kappa B, and activation of ion transporters, matricellular proteins, Aquaporin 4, and TLR4. The activation of these factors contributes to the development of brain edema, glutamate uptake, and other complications implicated in the pathogenesis of HE. However, the molecular events occurring in HE is not fully elucidated. We, therefore, examined a comprehensive gene expression profile by next-generation sequencing post-exposure of primary cultures of adult brain astrocytes to ammonia. Exposure of cells to ammonium chloride (NH4Cl) (0.5mM) for 48 hours showed increased expression of AMIGO3 (which is known to inhibit axon outgrowth and regeneration) and decreased expression of ASB1 and PEG3 (involved in p53-mediated cell death pathway and hypoxic/ischemic brain injury). However, exposure of cells to 5 mM NH4Cl displayed elevated levels of APOE (which may compromise Blood-Brain Barrier integrity and affect neuronal function), GPNMB (regulate astrocytic inflammatory response), H19 (known to regulate inflammation), and various mitochondrial genes, including MT-ND1-6, MT-ATP6, MT-ATP8, MT- CYB, MT-CO-1-3, and MT-RNR2 (involved in mitochondrial function). Pathway analysis has revealed connections with autophagy, lysosomal dysfunction, and ubiquitin-mediated proteolysis, indicative of a compelling astrocytic dysfunction with high doses of ammonia. Our findings suggest that ammonia may lead to neuronal dysfunction with lower concentrations, while higher doses may lead to central nervous system cell death.

Disclosures: R. Ramamoorthy: None. **N. Elumalai:** None. **A.M. Sanchez:** None. **H. Hussain:** None. **A.B. Rashed:** None. **R. Ruiz-Cordero:** None. **P. Chen:** None. **A.K. Carden:** None. **M.J. Paidas:** None. **A.R. Jayakumar:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR324.18/B67

Topic: B.09. Glial Mechanisms

Support: Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
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Larry L. Hillblom Foundation

Title: Stroke induces a pro-inflammatory gene module in astrocytes that is conserved in other neural injuries

Authors: *A. J. GLEICHMAN[1], R. KAWAGUCHI[2], M. V. SOFRONIEW[3], S. CARMICHAEL[4];
[1]Neurol., [2]UCLA, Los Angeles, CA; [3]UCLA Schl Med., Los Angeles, CA; [4]Neurol., UCLA Sch. Med., Los Angeles, CA

Abstract: After stroke, the primary cause of adult-onset disability, most patients improve to some degree but do not fully recover. Strategies to limit damage by exclusively minimizing neuronal loss failed repeatedly in clinical trials, suggesting that a multicellular approach is necessary. Work in both the developing and injured brain has shown that astrocytes - roughly a third of the cells in the brain - are capable of influencing many of the processes necessary for plasticity and repair. Using mouse models of cortical and white matter ischemic stroke, we identified zones of reactive astrocytes based on combined phenotypic and morphologic analyses. We then used these zones to inform a transcriptomic analysis, profiling astrocytes in varying proximity to the infarct border. Using Weighted Gene Correlation Network Analysis (WGCNA), we identified a module of genes whose expression correlates with proximity to the infarct border in both cortical and white matter stroke. These genes are predominantly involved in immune responses. Expression of these module genes after stroke correlates with astrocytic expression after other types of CNS injury and inflammation, suggesting a conserved core astrocytic transcriptomic response.

Disclosures: A.J. Gleichman: None. **R. Kawaguchi:** None. **M.V. Sofroniew:** None. **S. Carmichael:** None.

Poster

PSTR324: Astrocytes and Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR324.19/B68

Topic: B.09. Glial Mechanisms

Support: NIH Grant R01DA047157
VA 1I01BX005114

Title: Astrocytes-to-neurons interaction mediated by astrocytes-derived miRNA-16-5p: A preliminary study

Authors: J. GU[1,2], H. YI[1,2], X. ZHU[1], S. LIU[1], ***S. HAO**[1,3];
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Abstract: Exosomes derived from astrocytes can contain various biomolecules, including proteins, lipids, mRNAs and microRNAs (miRNAs). MiRNAs bind to their complimentary sequences of the 3′UTR region of target mRNAs to modulate gene expression by either inhibiting mRNA translation or inducing mRNA degradation. The significance of miR-16-5p in exosomes derived from activated astrocytes in the astrocytes-neuron interaction remains unclear. Mitochondrial sirtuin 3 (Sirt3) is an NAD+-dependent deacetylase that regulates mitochondrial detoxification. Bioinformatics analysis showed that miR-16-5p pairs the 3' UTR of Sirt3 mRNA in rats and mice. Here we reported that activated astrocytes release exosomes carrying miR-16-5p interact with neurons to lower Sirt3 expression in vitro. In the preliminary study, DI-TNC1 astrocytic cell line and B35 neuronal cell lines were used. The astrocytic cells were treated with TLR4 agonists to activate them. Western blots was used for transcriptional factor NF-kB in the astrocytes; exosomes carrying miR-16-5p expression was measured in the cultured medium. Luciferase report assay was used to determine the *miR-16* gene transcriptional mechanisms. We found that TLR4 selective agonist KDO2 treatment increased NF-kB and miR-16-5p expression. Pretreatment with siRNA against rat TLR4 mRNA reduced TLR4 and NF-kB. Bioinformatic analysis shows that there is a NF-kB motif binding area in the *miR-16* gene promoter region. Luciferase report assay showed that activated astrocytes increased *miR-16* Luciferase expression. Mutant NF-kB motif binding area reversed the increased *miR-16* luciferase activity. MiR-16-5p mimic decreases Sirt3 expression in B35 neuronal cells. The preliminary data suggest that NF-kB plays an important role in miR-16 expression in TLR4-activated DI-TNC1 astrocytic cells, which may mediated Sirt3 loss in the neurons.

Disclosures: J. Gu: None. **H. Yi:** None. **X. Zhu:** None. **S. Liu:** None. **S. Hao:** None.

Poster

PSTR325: Oligodendrocytes: Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR325.01/B69

Topic: B.09. Glial Mechanisms

Title: Xk is a novel oligodendrocyte protein with a potential role in de/remyelination.

Authors: *G. K. TANTI[1], M. L. BRILL[2,3], S. KALLURI[1], R. SRIVASTAVA[1], G. LEPENNETIER[1], R. ÖLLINGER[4], S. S. AYACHIT[1], R. RAD[4], M. SCHIFFERER[5,6], T. MISGELD[7,8,6], B. HEMMER[1,6];
[1]Dept. of Neurol., [2]Inst. of Neuronal Cell Biol., Klinikum rechts der Isar, TU Munich, Munich, Germany; [3]Inst. of Neuronal Cell Biol., [4]Inst. of Mol. Oncology and Functional Genomics and Dept. of Med. II, Tech. Univ. Munich, Munich, Germany; [5]German Ctr. for Neurodegenerative Dis. (DZNE), Munich, Germany; [6]Munich Cluster for Systems Neurol. (SyNergy), Munich, Germany; [7]Inst. of Neuronal Cell Biol., Munich, Germany; [8]Munich, Germany Munich Cluster for Systems Neurol. (SyNergy), Munich, Germany

Abstract: Oligodendrocytes, facilitate axonal insulation via myelination and remyelination. In demyelinating disorders like multiple sclerosis (MS), remyelination is hindered, yet the underlying mechanisms are not fully understood. Our research sought to identify new oligodendrocyte genes that might provide targets for remyelination therapies in MS. We conducted bulk RNA sequencing on premature oligodendrocytes, microglia, and endothelial cells from adult pig brains. We identified a number of new cell-type-specific genes and confirmed their expression with real-time PCR and western blot analysis. Among these potential cell type-specific genes, we identified XK, a gene transcribed from the X chromosome, which acts as a Kell blood group antigen. XK's association with Macleod Syndrome (MLS), characterized by distinctive red cell anomalies and neurological deficits, suggests that XK also plays a crucial role in the CNS. We found XK to be highly expressed in oligodendrocytes and, to a lower extent, in neurons. XK was co-expressed with VPS13A in oligodendrocyte, suggesting that XK is important for lipid transport and membrane equilibrium. In line with this finding, CRISPR/Cas-9 mediated XK knockout in oligodendrocytes led to apoptosis in cultured oligodendrocytes and brain slices, with a subsequent delay in remyelination in slice cultures. These insights reveal XK's potential as a therapeutic target for demyelinating diseases, including MS. Our findings enhance the understanding of myelination processes and suggest new therapeutic pathways.

Disclosures: G.K. Tanti: None. **M.L. Brill:** None. **S. Kalluri:** None. **R. Srivastava:** None. **G. Lepennetier:** None. **R. Öllinger:** None. **S.S. Ayachit:** None. **R. Rad:** None. **M. Schifferer:** None. **T. Misgeld:** None. **B. Hemmer:** None.

Poster

PSTR325: Oligodendrocytes: Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR325.02/B70

Topic: B.09. Glial Mechanisms

Support: JST SPRING JPMJSP2155

Title: Ube3a deficiency in oligodendrocyte precursor cells leads to abnormal myelination.

Authors: *X. LIU, M. FUJITANI, Y. OTANI;
Dept. of Anat. and Neurosci., Shimane Univ., Izumo, Japan

Abstract: The mutation of maternal ubiquitin-protein ligase E3A (*UBE3A*) gene causes Angelman syndrome (AS), characterized by severe neurodevelopmental disorder, intellectual disability, seizures, ataxia, and autism-like symptoms. Despite the inheritance of the *UBE3A* from both maternal and paternal sources, the paternal allele is silenced via genomic imprinting in central nervous system (CNS) neurons, resulting in exclusive maternal expression of *Ube3a* in these cells. Conversely, in glial cells such as astrocytes or oligodendrocytes, both maternal and paternal alleles of *Ube3a* are expressed in mice. Studies have reported reduced white matter volume and decreased myelin content in the brains of AS patients and AS model mice. Although glial expression of UBE3A is relatively low, abnormalities in oligodendrocytes may contribute to AS pathogenesis. We discovered biallelic expression of *Ube3a* in oligodendrocyte lineage cells, including oligodendrocyte precursor cells (OPCs) and mature oligodendrocytes. Subsequently, we evaluated the thickness of corpus callosum and cortex, and G-ratio, the ratio of the inner-to-outer diameter of a myelinated axon, in wild-type, *Ube3a* maternal-deficient (mKO), *Ube3a* paternal-deficient (pKO), and biallelic-deficient (full KO) mice. We observed significantly reduced thickness in the cortex and corpus callosum of *Ube3a* mKO and full KO mice, along with a significant decrease in mature oligodendrocytes, not OPCs, in the corpus callosum of these mice. Thus, UBE3A deficiency delayed the differentiation of corpus callosum OPCs into mature oligodendrocytes, leading to cortical hypomyelination. Furthermore, we found that neuronal UBE3A, rather than UBE3A in oligodendrocytes, may influence myelin thickness. Additionally, UBE3A in oligodendrocytes contributes to dysmyelination and an increased inner tongue area. UBE3A deficiency inhibited the differentiation of OPCs into mature oligodendrocytes rather than OPC proliferation. Consequently, UBE3A deficiency in oligodendrocyte lineage cells results in abnormal myelination.

Disclosures: X. Liu: None. **M. Fujitani:** None. **Y. Otani:** None.

Poster

PSTR325: Oligodendrocytes: Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR325.03/B71

Topic: B.09. Glial Mechanisms

Support: Robert E & Evelyn McKee Foundation Grant

Title: NG2-glia alterations in aging and major depressive disorder

Authors: *D. SOTELO, J. VARGAS MEDRANO, P. M. THOMPSON;
Texas Technol. Univ. Hlth. Sci. Ctr. El Paso, El Paso, TX

Abstract: Major depressive disorder (MDD) is the most prevalent psychiatric condition and is often associated with neuroinflammation, diminished glial cell density, and impaired myelination. While previously recognized primarily for their involvement in oligodendrocyte lineage, neural/glial antigen 2 (NG2) cells are now acknowledged for their multifaceted role in neuroinflammatory responses and maintenance of the neuronal environment. However, the majority of this evidence comes from animal models and non-invasive imaging. It remains unclear how these findings compare to research done in human brain tissue. This study aimed to identify alterations in proteins related to the physiology of aging and MDD. Using Western blot analysis, we measured protein levels for oligodendrocyte progenitor cells, NG2, inflammatory markers, interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), the hepatocyte growth factor (HGF), and a neuronal viability marker, B-cell lymphoma 2 (Bcl-2) in postmortem dorsolateral prefrontal cortex (dLPFC) of those with major depressive disorder (MDD) across adulthood and normal controls (NC). Ages of donors ranged from 30 to 90 years old. All Western blots were imaged, quantified, and analyzed by LI-COR Odyssey and Image Studio (LI-COR Biotechnology). To analyze levels of proteins throughout aging, simple linear regressions were performed with GraphPad Prism 9 ($p<0.05$). In NC, levels of NG2, and HGF increased in a linear relation with age β=0.003 ($F(1,6)=10.72$, $p=0.02$) $R^2= 0.68$, β=0.001 ($F(1,6)=10.82$, $p=0.01$) $R^2 = 0.64$, and Bcl-2 approached significance following a similar trend. Neuroinflammatory biomarkers, IL-1β and TNF-α, decreased in a negative linear relationship with age β=-0.004 ($F(1,6)=32.79$, $p=0.001$), $R^2 =0.84$, β=-0.001 ($F(1,6)=13.64$, $p=0.01$), $R^2 =0.69$. Contrastingly, the MDD group showed the opposite findings. Levels of IL-1β and TNF-α were significantly increased in MDD β=0.010 ($F(1,5)=7.72$, $p=0.03$) $R^2 = 0.60$, β=0.010 ($F(1,5)=8.7$, $p=0.03$) $R^2 =0.63$ with age. In conclusion, our results suggest NG2 glia protein level may increase with age and modulate neuroinflammation, but this role is dysregulated in the MDD group.

Disclosures: D. Sotelo: None. **J. Vargas Medrano:** None. **P.M. Thompson:** None.

Poster

PSTR325: Oligodendrocytes: Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR325.04/B72

Topic: B.09. Glial Mechanisms

Title: Evaluation by spatial transcriptome of oligodendrocyte lineages in animals subjected to the neonatal hypoxia-ischemia model

Authors: *R. B. FABRES[1], S. ZHANG[2], S. SYNOWIEC[3], I. GOUSSAKOV[4], J. DUAN[5], A. DROBYSHEVSKY[6];
[1]Pediatrics, Northshore univeristyhealth, evanston, IL; [2]Dept. of Psychiatry, NorthShore Univ. HealthSystem, Evanston, IL; [3]NorthShore Univ. HealthSystem, Evanston, IL; [4]Pediatrics, NorthShore Univ. HealthSystem Res. Inst., Evanston, IL; [5]NorthShore Univ.

HealthSystem/University of C, Evanston, IL; [6]Pediatrics, NorthShore Univ. HealthSystems, Evanston, IL

Abstract: Neonatal hypoxia-ischemia (HI) affects 1-3 per 1,000 full-term births and remains a significant cause of long-term neurodevelopmental disability. White matter (WM) injury is one of the main features found in oxygen deprivation injury, which can lead cognitive delay and motor deficits. The myelin sheath is responsible for much of the brain's WM, surrounding axons and allowing efficient conduction of action potentials. Mature oligodendrocytes (OL), which synthesize and maintain myelination, also constitute a significant proportion of the brain's WM. In recent years, OL and the myelination process have become potential therapeutic targets to minimize the effects of oxygen deprivation on the central nervous system. However, it is still unclear how cells from different OL lineages are affected depending on their location in the brain after hypoxic-ischemic events. Therefore, this work aimed to evaluate the expression of genes from five (5) different types of OL in different regions of the brain using the spatial transcriptome technique, CosMx. For this study, mice (C57BL-6) aged 10 days (p10) were submitted to the HI model (Vannucci), which is based on permanent occlusion of the left carotid artery and exposure of the animals to a hypoxic atmosphere with 8% O_2/92% N_2 for 45 minutes. When the animals reached the age of p12 (48h after injury) and p20 the animals were euthanized and transcardially perfused. The brain was collected, post-fixed in 4% PFA overnight and dehydrated using an alcoholic series. After the brains were embedded in paraffin and then sectioned coronally (7 μm) using a microtome. Sections were collected on slides and sent for spatial transcriptome analysis for Nanostring company. The analysis was carried out using the RStudio software SEURAT package. We evaluated 920 genes in five different cell types of OLs, among these the progenitor form (OPC) to mature OL was evaluated. The corpus callosum, internal capsule and frontal cortex ipsilateral to the carotid occlusion were compared to contralateral side from the same animal. Our analysis demonstrated that among the OL types there were no genetic changes in the frontal cortex at any of the ages evaluated, however, in the WM regions, there were high differences in gene expression that appear to be accentuated as the animal ages. Among these differences we can highlight genes that involve migration and maturation of these cells, such as Elmo1, Epn2, Map4k4 and Mobp, as well as genes that involve communication between OL and neurons and myelin synthesis. Therefore, this study indicates the structures where there are genetic alterations in OL lineages and genes that are potential targets for treatment for HI.

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Poster

PSTR325: Oligodendrocytes: Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR325.05/B73

Topic: B.09. Glial Mechanisms

Support: NIH Grant R03AG087284

Title: Oligodendrocyte-derived carnosine protects the CNS from neuroinflammation

Authors: *G. SCHULZ, T. KLEIN, B. ELBAZ;
Northwestern Univ., Chicago, IL

Abstract: The lipid peroxidation byproduct acrolein, systematically named propenal, is a highly toxic aldehyde that exerts strong toxic effects upon its covalent binding to macromolecules such as proteins, RNA, DNA, and lipids. Detoxifying cellular mechanisms have evolved to quench acrolein and turn it into a non-toxic compound. Elevated levels of acrolein were found in the brains of Alzheimer's disease patients at the preclinical stage, suggesting that acrolein accumulation contributes to the early stages of disease pathogenesis. In the CNS, acrolein is quenched by carnosine. The enzyme Carnosine synthase 1(Carns1) catalyzes the formation of carnosine from β-alanine and histidine. Aging and neuroinflammation are associated with reduced levels of carnosine within the brain. Restoring carnosine levels via food supplementation alleviates age-related reductions in brain activity and neuroinflammation. Nevertheless, the specific role of oligodendrocytes in carnosine-mediated detoxification is unknown, partially due to the lack of appropriate experimental models. We have developed the Carns1 conditional allele, enabling us to ablate Carns1 in oligodendrocyte lineage cells. In our preliminary studies, we found that the enzyme Carns1 is expressed in the CNS solely by mature oligodendrocytes. Although carnosine is a ubiquitous metabolite in the body, we found that the oligodendrocyte-specific ablation of Carns1 dramatically reduces carnosine levels in the CNS. This data suggests that oligodendrocytes are the sole source of carnosine within the CNS. We then examined the role of carnosine in neuroinflammation using the EAE model. We found that reducing carnosine levels resulted in an increase of acrolein adducts, which mark damaged areas. This suggests that oligodendrocyte-derived carnosine protects the CNS from neuroinflammation. The next step in our study aims to explore further protective abilities of carnosine in models of aging and Alzheimer's disease.

Disclosures: G. Schulz: None. **T. Klein:** None. **B. Elbaz:** None.

Poster

PSTR325: Oligodendrocytes: Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR325.06/B74

Topic: B.09. Glial Mechanisms

Support: Neuratris
Arsep

Title: Accumulation of PFAS into the myelin sheath: Long-term consequences on myelin physiology

Authors: *B. ZALC;
Sorbonne Univ.; Inserm, CNRS, ICM, Paris Cedex 13, France

Abstract: Accumulation of PFAS into the myelin sheath: Long-term consequences on myelin physiology V. Valcarcel[1], L. Butruille[1], MS. Aigrot[2], B. Zalc[2#] & S. Remaud[1#1]*CNRS UMR 7221, Sorbonne University, Mus´eum National d'Histoire Naturelle, F-75005 Paris France*[2]*Sorbonne University, Inserm, CNRS, Institut du Cerveau, Pitié-Salpêtrière Hospital, F-75013 Paris, France#equal contribution*
Over the past 30 years an unexplained increased incidence in multiple sclerosis (MS) is observed in developed countries, suspected to be exacerbated by environmental factors. We questioned whether exposure to some persistent organic pollutants such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), could interfere with the process of myelin formation and remyelination. Our working hypothesis is that PFAS could accumulate in lipid-rich structures, such as myelin, thus disturbing myelin sheath integrity. Accordingly, we recently published using LC-MS/MS that PFOS – and to a lesser extent PFOA - accumulated into the myelin sheath of offsprings exposed to PFOS via the mother drinking water during late gestation and lactation. Using *ex vivo* and *in vivo* approaches, we also demonstrated that among PFAS tested, PFOS, but not PFOA, affects functional remyelination (Butruille et al., 2023). Here, we have explored the long-term impact of perinatal PFAS exposure on oligodendrogenesis, myelination and remyelination.First, we showed that perinatal PFOS exposure, but not PFOA, impairs neurogliogenesis within the adult subventricular zone and blocks OPC maturation in the corpus callosum. Second, as observed by transmission electron microscopy, myelin sheath thickness was decreased, and numerous aberrant ultrastructures were identified in the corpus callosum suggesting permanent alterations in myelin integrity and stability. To examine this possibility, we have developed an *in vitro* system based on the production of myelin giant unilamellar vesicles (GUVs), that allowed us to assess how PFAS incorporation into the myelin lipid bilayer affected the mechanical and biophysical properties of myelin sheath.In summary, our data demonstrate that perinatal exposure to PFOS, and in a lesser extent to PFOA, lead to permanent alterations in myelin physiology, potentially increasing susceptibility to myelin disorders such as multiple sclerosis.

Disclosures: B. Zalc: None.

Poster

PSTR325: Oligodendrocytes: Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR325.07/B75

Topic: B.09. Glial Mechanisms

Support: SynaptixBio Ltd.

Title: Impact of Tubb4a mutations on oligodendrocytes and neurons

Authors: *P. R. NAPIT[1], A. BHAGAVATULA[1], J. L. HACKER[1], R. P. BATES[1], A. TAKANOHASHI[1], S. SASE[1], A. VANDERVER[1,2];
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Abstract: Hypomyelination and Atrophy of the Basal Ganglia and Cerebellum (H-ABC) is a rare leukodystrophy resulting in progressive loss of neurological skills in childhood. It is caused by heterozygous mutations in *TUBB4A*, which encodes tubulin beta class IVA (TUBB4A). Representing 10% of leukodystrophies, the p.Asp249Asn (D249N), a recurring variant in TUBB4A, results in cell-autonomous deficits in oligodendrocytes (OLs), medium spiny neurons, and cerebellar granule neurons. *TUBB4A*, a subtype of β-tubulins, heterodimerizes with α-tubulin to form microtubules (MT). MTs are essential for neuronal and OL structure, function, and cellular transport of critical proteins. In this study, we sought to determine how *Tubb4a* mutation causes OL deficits. Oligodendrocyte precursor cells (OPCs) generated from *the Tubb4a^{D249N} mice* failed to differentiate into OLs. The few differentiated mutant OLs exhibited impaired morphology and reduced myelin proteins (proteolipid (PLP) and myelin basic protein) as compared to the controls. Furthermore, isolated *Tubb4a* mutant OLs demonstrated reduced lysosomal puncta and aberrant mitochondrial puncta on OPCs and PLP+ OLs. *In vivo* electron microscopy in these mice supported the disrupted mitochondrial morphology and abnormal accumulation of lysosomes in axons and OLs. Ongoing studies are focused on understanding if *Tubb4a* mutation impacts the transport of these key organelles. This study highlights how the *Tubb4a* variant alters the fundamental cellular functions.

Disclosures: P.R. Napit: None. **A. Bhagavatula:** None. **J.L. Hacker:** None. **R.P. Bates:** None. **A. Takanohashi:** None. **S. Sase:** None. **A. Vanderver:** 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.; Takeda, Shire, Sanofi, Affinia, Ionis, Eli Lilly, Boehringer ingelhiem, Biogen, Sana, SynaptixBio, Orchard, Passage bio, Homology, NINDS, NCATS, PMD Foundation, H-ABC Foundation, AGSAA. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Myrtelle, Homology, Takeda, Eli Lilly. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); License for AGS Severity Score, AGS newborn screening and diagnostic biomarkers, ASO therapy in H-ABC.

Poster

PSTR325: Oligodendrocytes: Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR325.08/B76

Topic: B.09. Glial Mechanisms

Support: NSF Award #1938059 to A. Flores-Bonilla
Spaulding-Smith Fellowship to A. Flores-Bonilla

NIH NIAAA R01AA024774 to H.N. Richardson
IALS Midigrant to H.N. Richardson
CNS Seed-Bridge funding to H.N. Richardson

Title: Voluntary alcohol consumption and cognition in aged female mice

Authors: *M. SCHMITT[1], A. FLORES BONILLA[3], J. HAIRSTON[1], J. HARDY[1], O. ALPIZAR[1], E. NAUGHTON[1], E. M. VAZEY[4], H. N. RICHARDSON[2];
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Abstract: Aging is associated with cognitive decline and a reduction of frontotemporal corticocortical white matter tracts. In 2022, 18.4% of those aged 60-64 and 9.7% of those 65+ reported binge drinking alcohol within the previous month. Heavy alcohol use in older populations may accelerate the loss of white matter and worsen cognitive functioning, impacting other diseases of aging including frontotemporal dementias. Oligodendrocytes (OLs) are the myelinating cells of the central nervous system, wrapping axons in the protein-lipid rich myelin sheath, speeding up signal transduction. To begin exploring the relationship between binge drinking, cognition, and OLs in older adults we tested cognitive and drinking behaviors in a double transgenic mouse reporter line that conditionally tags OL precursor cells (OPCs) with enhanced yellow fluorescent protein (eYFP) following tamoxifen administration. Seventeen-month-old Pdgfr alpha-CreER^{TM}-eYFP mice (N=14) were tested for baseline cognitive functioning using the object location and novel object recognition tasks (OL/NOR). They were then injected with tamoxifen to induce Cre-recombination, followed by 10 weeks of voluntary ethanol (unsweetened 20%v/v) (n=7) or water (n=7) using a drinking in the dark (DID) model. Post-drinking OL/NOR testing was done one week following the last bout of drinking. We found that voluntary alcohol intake increased over the 10-week DID period, with individual average alcohol consumption ranging from 2.02ml/kg to 11.65ml/kg per session with a group average of 6.73 ± 3.31 ml/kg. The water group consumed from 7.74 ml/kg to 27.38 ml/kg per session with a group average of 18.53 ± 6.17 ml/kg. Baseline 24-hour NOR performance showed a robust correlation with average alcohol intake, with worse performing mice showing greater voluntary alcohol intake. Conversely, baseline levels of short-term location or recognition memory did not predict subsequent alcohol intake and those drinking levels did not relate to future cognitive performance on the OL/NOR tasks (post-alcohol). Immunohistochemical experiments using a combination of cellular markers are being used to determine if lower cognitive abilities and higher drinking are associated with delays in oligodendroglial differentiation and maturation. These experiments will help shape future studies identifying predictors and consequences of late in life alcohol use.

Disclosures: M. Schmitt: None. **A. Flores Bonilla:** None. **J. Hairston:** None. **J. Hardy:** None. **O. Alpizar:** None. **E. Naughton:** None. **E.M. Vazey:** None. **H.N. Richardson:** None.

Poster

PSTR325: Oligodendrocytes: Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR325.09/B77

Topic: B.09. Glial Mechanisms

Support: NSF Award #1938059
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NIH NIAAA R01AA024774
IALS Midigrant
CNS Seed-Bridge

Title: A history of adolescent drinking increases myelination of axons within the corticotropin releasing factor-enriched subregion of the central amygdala in adult mice

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Abstract: In the United States, approximately 11.1 million 12-25-year-olds reported binge drinking in 2022. Adolescent brains undergo substantial changes in neurocircuitry as oligodendrocytes (OLs) rapidly myelinate active axons which facilitates faster propagation of action potentials. The central amygdala (CeA) is enriched with cells expressing the stress response modulator corticotropin-releasing factor (CRF) peptide. Alcohol increases CeA cell activity and inhibiting CRF signaling in the CeA decreases alcohol consumption. Escalation in alcohol drinking has also been linked to genes involved in OL differentiation and myelin. A goal of this study is to understand how CRF and OLs may interact to affect alcohol drinking. We hypothesize that adolescent alcohol impacts the myelination of axons coming into and leaving the CeA. We used NG2-CreER^{TM}; Tau-mGFP male and female transgenic mice to tag differentiating OLs with membrane-bound green fluorescent protein (GFP) and track the formation of new (*de novo*) myelin sheaths during adolescence. Following tamoxifen-induced Cre-recombination on postnatal days (P) 21-24, mice had access to water (n=5/sex) or alcohol (unsweetened 20%v/v) (n=4-5/sex) using a drinking-in-the-dark voluntary binge drinking model throughout early adolescence (P28-42). Drinking significantly escalated in the two weeks of access (t-test, $p < 0.05$), with an average alcohol consumption of 3.3 ± 0.4 g/kg/4h in the first week and 4.6 ± 0.3 g/kg/4h in the second week. Mice were perfused and brains were collected after two months of abstinence. Brains were processed for immunohistochemical co-labeling of GFP and CRF proteins and counterstained with the fluorescent nuclear marker Hoechst. Confocal images were acquired using the CREST-V2 at 60X oil magnification with z-stacks of the CeA. CRF peptide expression was found higher in the CeA of females compared to males (main effect of sex, $p < 0.05$). We also found evidence for *de novo* myelin sheaths (GFP+ fibers) in the CeA during adolescence and early adulthood in all groups. *De novo* myelination was higher in the alcohol group compared to water group only in males (treatment x sex interaction and Bonferroni *post-hoc* analysis, ps < 0.05). These findings suggest alcohol impacts stress circuitry by increasing *de novo* myelination of axons interacting with CRF cells in the CeA.

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Poster

PSTR325: Oligodendrocytes: Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR325.10/B78

Topic: B.09. Glial Mechanisms

Support: PD/BD/150343/2019 (FCT)
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EMBO Scientific Exchange Grant - PGN 10018
IBRO Early Career Award
HORIZON-WIDERA-2023-ACCESS-04-01 under grant agreement 101160180 (PANERIS)

Title: Unlocking oligodendrogenesis and cognitive enhancement via neurotrophic factors and physical activity: integrating in vitro and in vivo approaches

Authors: *J. MATEUS[1,2], J. B. MOREIRA[1,2], A. BARATEIRO[3,4], S. OLIVEIRA[1,2], T. COSTA-COELHO[1,2], S. VAZ[1,2], B. SANTOS[1,2], D. M. LOURENCO[1,2], A. M. SEBASTIAO[1,2], A. M. FERNANDES[3,4], N. DAWSON[5], S. XAPELLI[1,2];
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Abstract: Oligodendrocytes (OL) are the myelin-forming cells in the Central Nervous System. The role of Adenosine A2A receptors (A2ARs) and brain-derived neurotrophic factor (BDNF) on adult oligodendrogenesis from subventricular zone neural stem cells (SVZ-NSCs) remains unknown. We aimed at first studying how these modulators and their putative crosstalk can influence OL differentiation from postnatal SVZ-NSCs. Results show that after 2 days in vitro (DIV), BDNF potentiated mRNA expression levels for OPC markers (N=3) in SVZ-derived neurospheres, while protein expression remained unaltered (N=3), an effect blocked by the A2AR antagonist ZM 241385 (N=3). The effects of BDNF in promoting SVZ-NSCs differentiation into OPCs were maintained throughout DIV 7 (N=9) and DIV 14 (N=3). At DIV 14 BDNF also promoted SVZ-NSCs differentiation into mature OL (N=5), an effect again blocked by ZM 241385 (N=5). Furthermore, Sholl analysis of mature OL also revealed that BDNF can lead to morphological alterations in OL, having distinct effects at different timepoints: at DIV 7 (N=52-59 cells) BDNF led to a reduction in ramification complexity, whereas at DIV14 (N=45-48 cells) co-treatment of BDNF with A2AR antagonist resulted in

increased cellular ramification. Importantly, this outlined a time-sensitive role for BDNF in promoting the expression of OPC mRNA markers in the beginning, followed by enhanced OPC and OL differentiation from SVZ-NSCs, which may be crucial in demyelinating disorders. Then, we explored how physical exercise (PE), by upregulating BDNF levels, could potentiate adult oligodendrogenesis in the cuprizone (CPZ) mouse model of demyelination. Our data shows that CPZ animals subjected to PE present a rescue in brain connectivity similar to control animals in the hippocampus, particularly in the dorsal hippocampal region (N=6-8). Long-term hippocampal memory impairments induced by CPZ were also recovered by PE, as observed with the NOR test (N=13-15). Additionally, preliminary electrophysiological studies showed a tendency for recovery in long-term potentiation in exercised CPZ mice (N=3-4). In conclusion, BDNF promotes the formation and differentiation of OPCs and OLs derived from SVZ-NSCs in vitro and this effect is partially blocked by the treatment with an A2AR antagonist. Moreover, PE can rescue CPZ-induced memory impairments and various of the inter-regional connectivity dysfunctions observed. Ultimately, we expect to identify PE as a potential inducer of adult oligodendrogenesis and remyelination, restoring brain connectivity and cognition in MS, through neurotrophic factor signaling.

Disclosures: J. Mateus: None. **J.B. Moreira:** None. **A. Barateiro:** None. **S. Oliveira:** None. **T. Costa-Coelho:** None. **S. Vaz:** None. **B. Santos:** None. **D.M. Lourenco:** None. **A.M. Sebastiao:** None. **A.M. Fernandes:** None. **N. Dawson:** None. **S. Xapelli:** None.

Poster

PSTR325: Oligodendrocytes: Disease Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR325.11/B79

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: The Charles M. Vallee Foundation for Long-COVID Research
The University of Miami Team Science Funding Program
Muriel, Murray, and Robert Smith Foundation
The University of Miami Miller School of Medicine

Title: Glioblastoma growth inhibition by viral coinfection in vitro

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Abstract: We investigated the effect of SARS-CoV-2 on cell metabolic activity in glioblastoma with and without other viral infections, which will demonstrate the impact of SARS-CoV-2 on tumor growth. C6 Glioma (rat glioblastoma cell line) was treated with various concentrations of SARS-CoV-2, HCV, and HIV nucleocapsid proteins, as viral particles have been shown to cause

cell injury in vitro and in vivo. Viable metabolically active cells were measured using a cell proliferation assay. Data was analyzed using Tukey's multiple comparisons test using GraphPad 9.5.1 software and presented as % change in metabolically active cells. Exposure of C6 Glioma to 500 ng of SARS-CoV-2 nucleocapsid led to a 19.2% decrease in metabolically active cells compared to the control ($p=0.002$). Similarly, exposure of these cells to 500 ng recombinant Hepatitis C Virus nucleoprotein led to a 35.7% decrease in metabolically active cells compared to control ($p<0.0001$). However, exposure of C6 cells to the combination of SARS-CoV-2 and HCV resulted in a 37.3% decrease in metabolically active cells compared to control ($p<0.0001$). Exposure of C6 Glioma to 500 ng recombinant HIV1 p24 nucleoprotein of HIV led to a 13.9% decrease in metabolically active cells compared to control ($p=0.0153$). However, exposure of C6 cells to the combination of SARS-CoV-2 and HIV led to a 39.3% decrease in metabolically active cells ($p<0.0001$). Exposure of C6 Glioma to SARS-CoV-2 nucleocapsid led to a 6.4% decrease in metabolically active cells as compared to exposure to HIV ($p=0.77$). Coinfection with 500 ng of SARS-CoV-2 and 500 ng of HIV led to a 24.8% and 29.5% decrease, respectively, in metabolically active cells than exposure to SARS-CoV-2 or HIV alone ($p = 0.0001$ and $p<0.0001$ resp.). Exposure of C6 Glioma to SARS-CoV-2 nucleocapsid led to a 25.4% increase in metabolically active cells compared to exposure to HCV ($p=0.0023$). Coinfection with 500 ng of SARS-CoV-2 and 500 ng of HCV led to a 22.3% decrease in metabolically active cells than infection with 500 ng SARS-CoV-2 alone ($p = 0.0006$), but only a 2.6% decrease in metabolically active cells than infection with 500 ng HCV alone ($p = 0.998$). Exposure of C6 Glioma to viral particles showed a significant decrease in metabolically active cells. Additionally, coinfection with SARS-CoV-2 and HIV showed a remarkable reduction in active cells. This suggests that SARS-CoV-2, in combination with HIV, may have a synergistic effect in reducing glioblastoma growth. Coinfection of SARS-CoV-2 and HCV did not lead to a significant change in metabolically active cells from primary infection with HCV alone, suggesting that the viruses act independently.

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Poster

PSTR326: Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR326.01/B80

Topic: C.01. Brain Wellness and Aging

Support: Award No. W81XWH-19-1-0329

Title: Calpain-2 Inhibition Stimulates Neurogenesis In Adult Mouse Brain

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Abstract: Neurogenesis takes place in the subventricular zone (SVZ) and in the dentate gyrus (DG) of the hippocampus of many adult mammalian species. It is a complex process and many factors have been shown to participate in its regulation. Recent findings indicate that calpain-2 could participate in neurogenesis regulation through the truncation of the transcription factor, Myeloid Ecotropic Viral Integration Site 2 (MEIS2) (Muller et al., 2024). MEIS2 is critical for nervous system development, including neuronal maturation and synaptogenesis. We recently reported the identification of NA-184, (S)-2-(3-benzylureido)-N-((R,S)-1-((3-chloro-2-methoxybenzyl)amino)-1,2-dioxopentan-3-yl)-4-methylpentanamide, as a selective calpain-2 inhibitor with neuroprotective properties (Baudry et al., 2024). Here, we report that acute treatment of adult mice with NA-184 results in an increased number of neurons immunopositive for Ki67, a marker of newly generated neurons, in both the SVZ and the DG. Treatment with NA184 resulted in increased levels of MEIS2 in these regions, as well as in other brain structures. Double-staining for Ki67 and MEIS2 indicates that many Ki67-positive neurons were also stained with MEIS2. Additionally, elevated levels of MEIS2 were found in cortex and hippocampus of conditional calpain-2 knock-out mice (CC2KO) with calpain-2 deletion in forebrain excitatory neurons. As MEIS2 has been implicated in synaptogenesis, we also analyzed the features of dendritic spines in hippocampal neurons of adult CC2KO mice. These neurons exhibited a decrease in the number of filipodia and thin spines and an increase in the number of mushroom and stubby spines, suggesting that calpain-2 deletion enhanced spine maturation. Overall, these results indicate that calpain-2 inhibition/deletion results in increased neurogenesis, as well as increased maturation of dendritic spines, potentially due to increased levels and activation of MEIS2. This could factor importantly in explaining the beneficial effects of calpain-2 inhibition following traumatic brain injury that we have previously reported (Wang et al., 2017, 2022). These findings could also contribute to the potential development of a calpain-2 inhibitor for the treatment of Alzheimer's disease (Arnsten and Baudry, 2023).

Disclosures: M. Baudry: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeurAegis, Inc. **T. Reece:** None. **X. Bi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeurAegis, Inc.

Poster

PSTR326: Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR326.02/B81

Topic: C.01. Brain Wellness and Aging

Support: Longevity Sciences from the National Center for Geriatrics and Gerontology, Japan (grant number 21-18 and 24-10)
Grants from Suntory Wellness Ltd.

Title: Positive association between the combination of open skill exercise with arachidonic acid or docosahexaenoic acid intake and brain volume changes among older community-dwelling Japanese individuals

Authors: *H. TOKUDA[1], C. HORIKAWA[1], Y. NISHITA[2], A. NAKAMURA[3], T. KATO[4], Y. KANEDA[1], T. IZUMO[1], Y. NAKAO[1], H. SHIMOKATA[5], R. OTSUKA[2];
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Abstract: A multifactorial lifestyle approach may be a more effective solution than a single-factor approach for maintaining brain health. Although brain atrophy precedes cognitive decline in older individuals, the effects of exercise combined with long-chain polyunsaturated fatty acid (LCPUFA) intake on brain atrophy remain unclear. In this study, we evaluated the association between exercise (open skill exercise [OSE] or closed skill exercise [CSE]) combined with LCPUFA (docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA], and arachidonic acid [ARA]) intake and brain volume changes among older Japanese individuals (n = 793, aged 60-88 years) without a self-reported history of dementia based on the datasets of a two-year longitudinal study. Brain volumes were measured using three-dimensional T1-weighted brain MRI with FreeSurfer at baseline and at follow-up. Exercise engagement and LCPUFA intake were divided into high and low groups according to frequency (>=once/month and <once/month) for OSE or CSE engagement and median LCPUFA intake according to sex, then categorized into four groups. The associations between multivariate-adjusted changes in brain volume and the combination of OSE or CSE with LCPUFA intake were assessed using a general linear model. Adjusted for confounding variables including age, sex, education, body mass index, medical history of hypertension, dyslipidemia, ischemic heart disease, stroke, diabetes, income, smoking status, alcohol consumption, physical activity, depressive tendency, and each brain volume at the baseline. Subgroup analysis was performed by restricting DHA and EPA intake (n = 263; median, 325 mg/d), similar to countries with low fish consumption, such as North America. In all participants in the analysis, the significant association between the four groups in total grey matter ($p = 0.028$) and frontal cortex ($p < 0.001$) volumes showed that the change (-4,105 and 174 mm^3) in the HIGH-OSE/HIGH-ARA group was cumulatively smaller than that in the HIGH-OSE/LOW-ARA (-5,939 and -556 mm^3), LOW-OSE/HIGH-ARA (-5,482 and -269 mm^3), and LOW-OSE/LOW-ARA (-7,328 and -882 mm^3) groups. In subgroup analysis, compared with the LOW-OSE/LOW-DHA^{sub} group (-9,533 mm^3), the HIGH-OSE/HIGH-DHA^{sub} group (-2,723 mm^3) cumulatively yielded a smaller decrease in total grey matter volume ($p = 0.002$). Therefore, our findings suggest that regular OSE with appropriate LCPUFA intake may contribute to the prevention of brain volume decrease in older individuals.

Disclosures: H. Tokuda: A. Employment/Salary (full or part-time):; Suntory Wellness Ltd. **C. Horikawa:** A. Employment/Salary (full or part-time):; Suntory Wellness Ltd.. **Y. Nishita:** None. **A. Nakamura:** None. **T. Kato:** None. **Y. Kaneda:** A. Employment/Salary (full or part-time):; Suntory Wellness Ltd. **T. Izumo:** A. Employment/Salary (full or part-time):; Suntory Wellness Ltd. **Y. Nakao:** A. Employment/Salary (full or part-time):; Suntory Wellness Ltd.. **H. Shimokata:** None. **R. Otsuka:** None.

Poster

PSTR326: Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR326.03/B82

Topic: C.01. Brain Wellness and Aging

Support: DoD VR220084

Title: Neurogenesis of RGCs and ERG recovery in a mouse glaucoma model after treatment with an alpha7 nicotinic acetylcholine receptor agonist.

Authors: *S. LUZADRE[1], D. M. LINN, Jr.[2], J. B. SPITSBERGEN[3], C. L. LINN[3]; [1]Western Michigan Univ., kalamazoo, MI; [2]Biomed. Sci., Grand Valley State Univ., Allendale, MI; [3]Biol. Sci., Western Michigan Univ., Kalamazoo, MI

Abstract: Experiments were performed to demonstrate ERG recovery in glaucoma-induced adult mice after neurogenesis of RGCs were induced following eye drop treatment with a selective alpha7 nicotinic acetylcholine receptor agonist, PNU-282987. Both sexes of adult mice (3-6 months) were injected with 1.2M hypertonic saline into the episcleral vein of anesthetized mice to increase IOP. One month after the procedure to induce glaucoma-like conditions, mouse eyes received daily eye drops containing 1mM PNU-282987/1mg/ml BrdU/1%DMSO. Weekly ERGs were recorded using the Celeris Diagnosys ERG System. At different time points, animals were euthanized, retinas were removed and processed with antibodies against BrdU and Thy 1.2, counterstained with DAPI, and viewed using a Nikon confocal microscope. Data was analyzed with ANOVA and differences were significant at P less than 0.05. N's between 5-12 were obtained under each condition. Hypertonic saline injections elicited a significant increase in IOP four weeks post injection (an average of 15.8 mmHg ±1.2) compared to an average of 11.2 mmHg (±1.8) measured from the same animals before the procedure. Induction of glaucoma also significantly reduced the cell density of Thy1.2+ RGCs by an average of 28.31% (±1.5) four weeks after injection. To illustrate the regenerative potential of PNU-282987, injected animals were treated with BrdU alone or with PNU-282987/BrdU. In the injected mice treated only with BrdU, no BrdU+ cells appeared in the RGC layer. However, after agonist treatment following saline injection, Thy1.2/BrdU+ neurons appeared in the GCL. After 2 weeks of agonist treatment, PNU-282987 significantly reduced the loss of Thy1.2+ cells associated with the glaucoma procedure to an average of only 2.4% (±0.8) compared to the near 30% average that are typically lost. In ERG recordings, the amplitude of the photopic PhNR decreased by 71.5% (±6.2) after the glaucoma procedure within 1 week. When treated with the agonist for 2 weeks, the amplitude of the PhNR recovered by 90% (±20.5). The amplitude of pERG (P1-N2) recordings significantly decreased by 67.8% (±9.2) after inducing glaucoma within 4 weeks but recovered to control values after treatment with PNU-282987 (an average of 103% (±8.5)). Scotopic oscillatory potential amplitudes (OP1, 2 and 3) decreased significantly by an average range of between 80.3 and 85.6% (±16.1) after the glaucoma procedure. After treated with the

agonist, all OPs recovered by an average range of 65 to 85% (±21.7). Results from these studies support the hypothesis that PNU-282987 induces neurogenesis in glaucoma-induced adult mice and provides recovery of the ERG PhNR, pERG and OP amplitudes.

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Poster

PSTR326: Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR326.04/B83

Topic: C.01. Brain Wellness and Aging

Title: Comparison of EEG Activity According to Efficiency in an Incidental Visuospatial Memory Task

Authors: *M. JUNCO MUÑOZ[1], A. TÉLLEZ-ANGUIANO[2], M. A. GUEVARA[3], M. CERVANTES[4], O. MEJÍA-RODRÍGUEZ[1], M. OLVERA-CORTES[1];
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Abstract: At a global level, a demographic transition in the population index is observed, leading to an increase in the prevalence of pathologies such as the deterioration of cognitive functions. Visuospatial episodic memory defined as the ability to recall autobiographical episodes and complex facts. It has been reported to be more vulnerable to age-related changes such as the loss of synaptic contacts and apoptosis, which alters the neural processes involved in communication between fronto-temporal brain regions. Evidence indicates that in diseases presenting dementia symptoms, these changes begin 7 to 10 years before clinical manifestations such as forgetfulness appear. We wondered if an incidental learning test challenging visuospatial memory skills could constitute a timely detection tool for cognitive decline. Furthermore, we evaluated the sensitivity of the test to show differences in the theta electroencephalogram (EEG) activity among adults over 50 years old, classified by their efficiency in the test. To address this, a cross-sectional, comparative, observational, and prospective study was conducted. Through a simple random sampling strategy, a sample of N:100 healthy participants aged 50-85 years (X:62.7; SD:10.28) was obtained. The inclusion criteria were a score of +26 points on the Montreal Cognitive Assessment Test (Version 07/11/04). Participants were classified by their efficiency in object-place associations recall, and baseline EEG activity at 4-8 Hz was recorded according to the international 10-20 system. We found that recall of the object-place visuospatial information association is more susceptible to errors than object recognition. EEG activity at 4-8 Hz under baseline conditions in participants with low efficiency in recalling incidentally learned object-place associations was higher than that of efficient participants in frontal and temporal derivations. These differences persisted when comparing by derivation (Fp1 U: -5.279; $p<0.001$;

FP2 U: -5.950; p<0.001; F3 U: -3.840; p <0.001; F4 U: -4.776; p<0.001; F7 U: -5.260; <0.001; F8 U: -3.572; p<0.001; T4 U: -4.992; p<0.001; T5 U: -4.001; p<0.001; T6 U: -4.833; p<0.001) except for the left temporal derivation (T3 U: -1.775; p<0.078) and when grouped by lobe (right frontal U: -4.174; p <0.001; left frontal U: -4.820; p<0.001; right temporal U: -3.138; p<0.002; left temporal U: -1.950; p<0.053). We conclude that the incidentally learned object-place association is a condition of episodic memory that could be used as an early detection tool for cognitive decline.

Disclosures: M. Junco Muñoz: None. **A. Téllez-Anguiano:** None. **M.A. Guevara:** None. **M. Cervantes:** None. **O. Mejía-Rodríguez:** None. **M. Olvera-Cortes:** None.

Poster

PSTR326: Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR326.05/B84

Topic: C.01. Brain Wellness and Aging

Support: Alzheimer's Association AARFD-21-853104
Bright Focus A2022048S
NIH_Goizueta ADRC P30 AG066511
NIH NINDS R01NS109226

Title: Frequency-specific non-invasive sensory stimulation neuroplastic adaptation in stressed mice

Authors: *T. C. FRANKLIN[1], M. GOODSON[2], H. ZEPEDA[2], S. BITARAFAN[3], N. KYE[2], J. KRAUS[2], A. PRICHARD[4], L. D. BRAUN[5], L. WOOD[3], A. C. SINGER[2];
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Abstract: Chronic stress promotes life-long risk for neuropsychiatric decline by increasing neuroimmune signaling and disrupting synaptic health and plasticity. We and others have demonstrated that non-invasive gamma sensory stimulation (flicker) modulates immune signaling and microglial function in male mouse models of Alzheimer’s disease and wild-type mice. However, no research to date has studied the effects of flicker in the context of stress. Accordingly, our goal for this study was to determine if flicker moderates neuropsychiatric-like behavioral deficits and mitigates glial and synaptic pathology following chronic stress. Male and female mice underwent daily audiovisual (AV) flicker intervention (10Hz, 40Hz or no stimulation control) and daily stress exposure for 28 consecutive days (C57BL6 mice; n=5-10/group per sex). The mice were tested for anxiety-like behaviors and anhedonia using a range

of behavioral assays. To identify cell-type specific genes modulated by AV flicker in chronically stressed mice, we quantified transcriptomic changes in $Thy1^+$ neurons, microglia, and astrocytes isolated from the frontal cortex. To determine how flicker mitigates stress-induced changes to glia and synaptic spines, we quantified spine density changes in Thy1-GFP mice. We measured glial morphology as an additional assay of microglial and astrocyte reactivity in the medial prefrontal cortex, a region that is highly sensitive to psychological stress. We found that stress-induced molecular changes in the frontal cortex are modulated in a sex-, and frequency-specific manner that coincides with behavioral resilience in stressed mice. We found that AV flicker significantly attenuates stress-induced behavioral and neurobiological alterations in chronically stressed animals with different optimal frequencies of stimulation for males and females. Our findings revealed that frequency-specific flicker intervention modulates both neuronal and glial cells at the transcriptional level to promote significant regulation of translational, synaptic plasticity and neurotransmitter signaling pathways in stressed animals. In addition, we found that frequency-specific flicker intervention leads to the reorganization of cortical dendritic spines to enhance the proportion of plastic and dynamic filopodia and long thin spines in stressed male and female mice. Our findings show that frequency optimized flicker intervention improves stress pathology at multiple scales to promote neuroplastic adaptation in a sex- and frequency-specific manner. Thus, flicker may prevent neuropsychiatric health decline in conditions with sex dimorphic symptoms and prevalence.

Disclosures: T.C. Franklin: None. **M. Goodson:** None. **H. Zepeda:** None. **S. Bitarafan:** None. **N. Kye:** None. **J. Kraus:** None. **A. Prichard:** None. **L.D. Braun:** None. **L. Wood:** None. **A.C. Singer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Singer has a conflict of interest managed by an umbrella COI management plan, Cognito.

Poster

PSTR326: Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR326.06/B85

Topic: C.01. Brain Wellness and Aging

Support: DOD Grant W81XWH2110661

Title: Delayed treatment with Lacto-N-Fucopentaose III and/or inulin-supplemented diet ameliorates hippocampal synaptic transmission and plasticity deficits in a model of Gulf War Illness

Authors: *F. TEJEDOR-ROJAS, T. KALINOWSKI, B. HUDSON, N. M. FILIPOV, J. J. WAGNER;
Physiol. & Pharmacol., Univ. of Georgia, Athens, GA

Abstract: Gulf War Illness (GWI) is a chronic multi-symptom condition that affects approximately one-third of the U.S. military personnel deployed in the Persian Gulf War. Neurological, immunological, and gastrointestinal deficits feature prominently in GWI. We have shown that the immunomodulatory glycan Lacto-N-Fucopentaose III (LNFPIII) enhances gut health, improves neurogenesis, and has positive neurobehavioral and neurophysiological effects in preclinical GWI models. Inulin, a safe soluble fiber supplement to the diet, has been demonstrated to be beneficial for both gut and brain health in both aged mice and humans. Because LNFPIII improved some, but not all, behavioral deficits caused by GWI-related exposures, we examined whether the beneficial effects of LNFPIII on hippocampal long-term potentiation (LTP), a neurophysiological correlate for learning and memory, are augmented by an adjunct dietary treatment with inulin. In addition, the effects of inulin diet alone on synaptic transmission and synaptic plasticity were determined. To emulate GWI, we used a well-established preclinical model: Male C57BL/6J mice were exposed for 14 days to pyridostigmine bromide (PB) and N,N-Diethyl-3-methylbenzamide (DEET). In addition, corticosterone was administered via drinking water on days 8-14, and a single diisopropylfluorophosphate (DFP, a sarin surrogate) injection on day 15. Nine months after exposure, mice were randomly assigned to receive LNFPIII treatment, inulin-supplemented diet, or both. Mice were sacrificed, and *ex-vivo* hippocampal slice electrophysiology was performed twelve months after last day of exposure. Schaffer collaterals were stimulated in the CA1 and field excitatory postsynaptic potentials (fEPSPs) at the *stratum radiatum* were recorded to assess synaptic transmission and synaptic plasticity. Hippocampal LTP was decreased following GWI chemical exposure from 46 ± 1% to 25 ± 2% (mean ± SEM). Once again, we found that LNFPIII treatment alone restores this LTP deficit. Our new findings indicate that inulin diet by itself ameliorates the effects of GWI chemical exposure on LTP (37 ±1%). Treatment with the combination of LNFPIII and inulin diet further increased hippocampal LTP. These results indicate that an inulin-supplemented diet plays a restorative role in synaptic plasticity after GWI chemical exposure. Furthermore, dietary inulin shows promise as an adjunct therapeutic. This is indicated by the superior ameliorative capacity of combined LNFPIII and inulin treatment on hippocampal LTP in a well-established mouse model of GWI, suggesting that evaluation of these therapeutics in a clinical setting is warranted.

Disclosures: F. Tejedor-Rojas: None. **T. Kalinowski:** None. **B. Hudson:** None. **N.M. Filipov:** None. **J.J. Wagner:** None.

Poster

PSTR326: Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR326.07/B86

Topic: C.01. Brain Wellness and Aging

Support: Florida Department of Health, Ed and Ethel Moore Alzheimer's Disease Research, Grant #21A12

Title: Transient Exercise-Induced Changes of Circulating Factors in the Mouse Muscle-Brain Axis

Authors: *C. WANG[1], J. JUERGENSMEYER[2], K. ALVIÑA[3];
[1]Dept. of Neurosci., Univ. of Florida, Gainesville, FL; [2]Neurosci., Univ. of Florida, Gainesville, FL; [3]Neurosci., Univ. of Florida Dept. of Neurosci., Gainesville, FL

Abstract: Exercise promotes healthy cognitive aging and could be an effective non-pharmacological alternative to prevent or delay pathology associated with neurodegenerative disorders. However, mechanisms underlying such positive effects are not fully understood. Irisin, a myokine that is secreted from skeletal muscle during exercise, is linked to mechanisms that become dysfunctional as we age, such as glucose metabolism and hippocampal neurogenesis. Nevertheless, there have been contradictory reports on changes in irisin levels following exercise. Such inconsistencies might be a result of variability in experimental conditions, such as duration of exercise protocols (e.g., acute or chronic) and/or timing of tissue collection (e.g. immediately after or hours later). To determine the precise timespan of exercise-induced changes in circulating irisin, we designed exercise protocols that tested the effect of these experimental variables. We hypothesized that changes in circulating irisin concentration occur during or immediately after exercise and return to baseline shortly thereafter. To test this hypothesis, we subjected adult male and female mice to swimming or running exercise for 20 min and measured post-exercise serum irisin concentration (via ELISA) at: 0, 30, 60, or 120 min after. Compared to sedentary controls, we observed a ~20% increase in male mice immediately after either exercise protocol, which decreased to baseline levels within 60 min. No changes were detected in female mice. Next, we performed a chronic exercise protocol (swimming for 20min/ day for 21 days) with a separate group of male and female mice, and measured serum irisin 24 h after the last exercise session. As expected, no difference was measured between the exercise group and the sedentary controls. Our results suggest that irisin is released during exercise and circulating levels return to baseline within an hour. Therefore, the timing of sample collection should be carefully considered to reliably detect exercise-induced changes in circulating irisin. In addition, we observed robust sex-dependent differences, including the potential relationship between Irisin release and stress.

Disclosures: C. Wang: None. **J. Juergensmeyer:** None. **K. Alviña:** None.

Poster

PSTR326: Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR326.08/B87

Topic: C.01. Brain Wellness and Aging

Support: CONAHCYT

Title: Anticonvulsivant effect of Cannabidiol alone or in combination with dapsone in epilepsy rat model.

Authors: *D. ISLAS DIAZ[1], C. RIOS[2], V. BARON-FLORES[1], A. RUIZ[1], M. ISLAS[3], A. MATA-BERMUDEZ[4], M. MENDEZ-ARMENTA[5], A. DIAZ-RUIZ[6];
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Abstract: Epilepsy is a condition affecting the central nervous system characterized by abnormal and recurrent brain activity, often leading to seizures, behavioral changes, or unusual sensations. The delicate balance between excitatory and inhibitory neurotransmitters is crucial for maintaining normal neuronal function. When there is an excessive release of glutamate, it stimulates NMDA receptors, causing an influx of calcium ions that disrupt cellular homeostasis. This imbalance triggers cytoplasmic enzyme activation and increases nitric oxide production, resulting in the generation of free radicals that damage DNA and ultimately lead to nerve cell death. In this study, an alternative treatment involving cannabidiol and dapsone, either alone or in combination, is proposed to investigate their potential anticonvulsant, neuroprotective, and antioxidant properties in a rat model of epilepsy induced by pentylenetetrazole. The project aims to establish and characterize the behavioral aspects of the epilepsy model, assess the antioxidant effects, and evaluate markers of cell death through apoptosis. Standardized tonic-clonic seizure crises were induced, and isobolographic analysis was performed to determine the combined doses of the drugs. Interestingly, the combination doses did not significantly alter seizure latencies compared to individual drug administrations. However, the groups treated with dapsone and cannabidiol showed a significant decrease in lipid peroxidation compared to the untreated group, suggesting a potential for reducing oxidative stress. Additionally, the concentration of reduced glutathione increased significantly in the treated groups, indicating a protective effect on cellular components.Furthermore, the activity of caspase enzymes was evaluated, with notable differences observed in the groups receiving the combination treatment, suggesting a possible neuroprotective or anti-apoptotic effect of the combination therapy. Overall, the results suggest that the combination of dapsone and cannabidiol at specific doses exhibits neuroprotective, anti-apoptotic, and antioxidant effects in the epilepsy model. Ongoing immunohistochemical studies aim to further elucidate the neuroprotective mechanisms involved.

Disclosures: D. Islas Diaz: None. **C. Rios:** None. **V. Baron-Flores:** None. **A. Ruiz:** None. **M. Islas:** None. **A. Mata-Bermudez:** None. **M. Mendez-Armenta:** None. **A. Diaz-Ruiz:** None.

Poster

PSTR326: Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR326.09/Web Only

Topic: C.01. Brain Wellness and Aging

Title: Dual spectrum photobiomodulation stimulation improves cognitive performance as measured by the EEG-ERP oddball paradigm.

Authors: *I. STRICKLAND[1], D. OAKLEY[2], A. PARIEVSKY[3];
[1]Medify Inc., Marina Del Rey, CA; [2]WAVi, Boulder, CO; [3]IDDRC, Semel Inst. for Neurosci. and Human Behavior, BRI, UCLA, Los Angeles, CA

Abstract: Age-related decline in cognitive performance is well documented. Losing the ability to process information and make decisions effectively harms one's social independence and is directly linked to age-associated diseases. This open-label study aims to objectively investigate how dual-spectrum, multi-wavelength photobiomodulation can affect cognitive performance as measured using EEG-Event-related potentials (ERPs). This dual-spectrum therapeutic approach targets at least two biochemical processes, including increased mitochondrial ATP levels and activation of light-sensitive ion channels. We used a novel dual-spectrum photobiomodulation intervention to stimulate the pre-frontal cortex of healthy participants (n=15, aged 26 - 68 years old) for 15 minutes with a spectrum of red and near-infrared light wavelengths spanning 633nm to 1070nm. Before, and immediately after the intervention, participants were subjected to EEG-ERP recordings, following the widely studied audio oddball P300 protocol. Measurements of ERP amplitude (P300V) and latency (P300T) reflect the brain's cognitive ability to recognise the different tones in a series of repetitive tones. ERP measurements provide objective biomarkers of the number of attentional resources devoted to a given task (P300V) and a measure of cognitive processing speed (P300T). In addition, we also measured changes in physical reaction time. The difference in pre-intervention and post-intervention EEG results were analysed using McNemar's test to evaluate the change in state to test the null hypothesis that the treatment had no effect. EEG-ERP results were classified as "above normal" or "below normal" based on previously published ERP and reaction time data sets. Before the photobiomodulation intervention, 3 participants were categorised as being above normal, but following the photobiomodulation stimulation this changed to 10 participants being categorised as being above normal. Initial statistical analyses calculated a chi-squared value of 3.8 and a P-value near our $P<0.05$ cut-off used to reject the null hypothesis that the treatment had no effect. The use of a dual-spectrum photobiomodulation intervention had a statistically significant effect on the cognitive capacity, processing speed, and reaction time of participants. The results of this study warrant further investigation into the prevention of natural age-related cognitive decline, recovery from traumatic brain injury, and age-related neurological disease, using photobiomodulation interventions.

Disclosures: I. Strickland: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Medify Inc..

Poster

PSTR326: Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR326.10/B88

Topic: C.01. Brain Wellness and Aging

Support: NRF-2019R1H1A2039693
NRF-2020R1I1A3071587

Title: A Pilot Study of Low Frequency Transcutaneous Vagus Nerve Stimulation and Transcranial Random Noise Stimulation

Authors: *E.-B. BAE;
Inst. of Liberal Educ., Incheon, Korea, Republic of

Abstract: To evaluate the feasibility of two forms of neuromodulation, transcutaneous vagus nerve stimulation (tVNS) and transcranial random noise stimulation (tRNS) were conducted for treating chronic tinnitus. A total of 24 tinnitus patients were enrolled, 11 for tVNS and 13 for tRNS. Both tVNS and tRNS led to significant reductions in tinnitus intensity, tinnitus distress, and Tinnitus Handicap Inventory scores 3 days after treatment, and these effects persisted for 1 month with no significant differences between the two treatments. The electroencephalogram data revealed a notable decrease in the power of the beta and gamma bands primarily in the auditory cortex on the opposite side of stimulation for both tVNS and tRNS. In the case of tRNS, the beta band power decrease was more widespread than tVNS, affecting the entire brain 3 days after treatment. Furthermore, this reduced activity continued for several electrodes up to 1 month after treatment. The correlation analysis indicated that tRNS maximized effects in 3 days after treatment. This study's results imply that tVNS and tRNS may have different mechanisms in neuromodulation, and address a way to develop tinnitus treatment in clinical practice.

Disclosures: E. Bae: None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.01/B89

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

Title: The neuroprotective ingredient in TeMac^{TM} ethyl acetate fraction prevents memory deficits in rats by targeting cholinergic enzymes and combating scopolamine-induced hippocampal alterations

Authors: *B. AKAMBA AMBAMBA, Jr;
Biochem., Univ. of Yaounde I Fac. of Sci., Yaounde, Cameroon

Abstract: Alzheimer's disease (AD) is associated with cognitive impairments which are linked to a deficit in cholinergic function. The objective of this study was to evaluate the ability of ethyl

acetate fraction TeMac^{TM} to prevent memory impairment in scopolamine-rats model of Alzheimer's disease and by *in silico* approaches to identify molecules in ethyl acetate fraction TeMac^{TM} inhibiting acetylcholinesterase. The cholinergic cognitive dysfunction was induced by intraperitoneal injection of scopolamine (1 mg/kg daily) in male *Wistar* rats for seven consecutive days. ethyl acetate fraction TeMac^{TM} at 400mg/kg body weight was orally administrated 60 minutes after scopolamine. Donepezil was used as a reference drug. The cognitive deficits were assessed by the Morris Water Maze and novel object recognition tests. After sacrifice, rat brains were harvested and used to carry out cholinesterase enzyme activity and histopathological analysis. A LC-MS characterization of the ethyl acetate fraction TeMac^{TM} was carried out and the identified molecules were tested *in silico* for their ability to cross the BBB and inhibit acetylcholinesterase using molecular docking. The administration of the ethyl acetate fraction TeMac^{TM} led to the prevention of memory deficits in rats by significantly reduced the cholinesterase enzymes activities and protection against morphological alterations and loss of neurons in hippocampus. Seven major compounds were identified in ethyl acetate fraction TeMac^{TM}. Molecular docking simulations confirm the ability of oleaterminaloic acid B and stigmasterol to cross the BBB and interact with peripheral site and the acyl pocket of acetylcholinesterase. All these observations suggest that ethyl acetate fraction TeMac^{TM} can therefore be used as an alternative for the management of AD-related cognitive impairments.

Disclosures: B. Akamba ambamba: None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.02/B90

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

Support: NIH grant RF1AG077484
NIH grant RO1AG054025
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Alzheimer's Association Grant AARF-22-967275
UTMB 2021 Claude D. Pepper OAIC Pilot grant

Title: Oral CL3, a novel curcumin derivative attenuates tau pathology and neuroinflammation, and enhances cognitive function in the 3XTG Alzheimer's disease mouse model.

Authors: *S. GAIKWAD[1], M. HAQUE[2], C. JEREZ[3], R. J. XAVIER[3], M. MONTALBANO[3], R. KAYED[3];
[1]Neurol., The Univ. of Texas Med. Br. at Galveston, GALVESTON, TX; [2]Univ. of Texas Med. Br., Galveston, TX; [3]Neurol., Univ. of Texas Med. Br., Galveston, TX

Abstract: Neurodegenerative tauopathies like Alzheimer's disease (AD) are characterized by tau protein accumulation and aggregate formation. Currently, there are no disease-modifying treatments available for these conditions. Soluble and hydrophobic tau oligomers are highly neurotoxic and contribute significantly to disease progression by initiating tau seeding and misfolding, leading to widespread tau pathology in the brain. Modulating tau oligomers with small molecules could be a promising therapeutic approach to target their toxicity independently of other factors involved in their formation. Previously, we demonstrated that a novel curcumin derivative, CL3, effectively modifies the aggregation of brain-derived tau oligomers (BDTOs) from various human tauopathies, forming non-toxic tau species and protecting neurons from BDTO toxicity, as well as reducing tau-seeding activities in vitro. In this study, we investigated the impact of oral CL3 treatment on tau pathology burden, neuroinflammation, and cognitive functions in aged 3XTG mouse model of AD. Mice received repeated oral doses of 20 mg/kg CL3 daily for a month, starting at 12 months of age, when tau-driven pathology is more pronounced. We found that CL3 colocalizes with pathological tau in brain tissues from human neurodegenerative tauopathies. Furthermore, oral CL3 treatment effectively reduced tau oligomer and Aβ pathology burden in the brain and improved cognitive performance in 3XTG mice. Mechanistic studies revealed that CL3 specifically reduced neuroinflammatory responses of microglia and astrocytes by inhibiting pathological cGAS-STING pathways. Together, these studies suggest that orally available CL3 mitigates Tau oligomers pathology and improve cognitive functions in AD mouse model.

Disclosures: S. Gaikwad: None. **M. Haque:** None. **C. Jerez:** None. **R.J. Xavier:** None. **M. Montalbano:** None. **R. Kayed:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer’s Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.03/B91

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

Support: MCIN/AEI/10.13039/501100011033 JDNL and LJD (grant number PID2020-115823-GBI00)
JCCM and ERDF A way of making Europe (grant number SBPLY/21/180501/000150) JDNL and LJD
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Title: Low dose of VU0810464, a selective GIRK channel activator, as a potential treatment to prevent hippocampal memory deficits in male and female mice of an early AD model.

Authors: *J. MULERO FRANCO[1], R. JIMÉNEZ-HERRERA[2], A. CONTRERAS[3], S. DJEBARI[2], J. D. NAVARRO-LOPEZ[4], L. JIMENEZ-DIAZ[5];
[1]Med. Sci., Univ. De Castilla La Mancha, Ciudad Real, Spain; [2]Neurophysiol. and Behaviour Lab., Univ. de Castilla La Mancha, Ciudad Real, Spain; [3]Neurophysiol. and Behaviour Lab., Univ. of Castilla la Mancha, Sch. of Med., Ciudad Real, Spain; [4]- Neurophysiol. and Behaviour Lab., Univ. de Castilla-La Mancha, Ciudad Real, Spain; [5]UCLM, Neurophysiol & Behav Lab., Univ. Castilla La-Mancha, Ciudad Real, Spain

Abstract: In addition to the accumulation of amyloid plaques and neurofibrillary tangles, the presence of increased neural activity is a characteristic feature of Alzheimer's disease (AD). It also serves as a prognostic indicator for the advancement of AD pathology and cognitive decline in individuals with mild cognitive impairment due to AD. Yet the mechanisms that drive such exaggerated hyperexcitability and their behavioral effects remain unclear. It is known that G-protein-gated inwardly rectifying potassium (GirK) channels control neural excitability in the hippocampus by the hyperpolarization in response to many G-protein-coupled receptors activation. Here, targeting hyperexcitability by using male and female mice of a model of early AD generated by oligomeric forms of amyloid-β ($A\beta_{1-42}$) peptide, we found that activation of G protein- gated inwardly rectifying K+ (GIRK) channels with the selective activator VU0810464 preserves: 1) at the synaptic level, CA3-CA1 long-term synaptic potentiation (LTP), and 2) at the behavioral level, the object location memory (OLM), a model of hippocampal-dependent spatial contextual recognition memory. Furthermore, we demonstrate these synaptic plasticity and OLM normalization effects in male and female mice of the early AD model with two (low and high) different VU0810464 dosages. However, in healthy animals, high dose of VU0810464 significantly disrupted LTP and OLM while low dose has no noticeable effects on both processes.We propose that the precise normalization of neural excitability with low dose of VU0810464 might be a promising strategy to prevent hippocampal upstreaming memory deficits in models of early stage of AD.

Disclosures: J. Mulero Franco: None. **R. Jiménez-Herrera:** None. **A. Contreras:** None. **S. Djebari:** None. **J.D. Navarro-Lopez:** None. **L. Jimenez-Diaz:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer’s Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.04/B92

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

Support: RGC/GRF 17102120
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NSFC/RGC/JRS N_HKU735/21
RGC/CRF C1024-22GF
RGC/CRF C7074-21G
HMRF 09200966

Title: The role of parvalbumin inhibitory interneuron in the early hippocampal pathogenesis of Alzheimer's disease

Authors: *W. XIE, C. S. LAI;
Sch. of Biomed. Sci., The Univ. of Hong Kong, Hong Kong, China

Abstract: Alzheimer's disease is a common neurodegenerative disorder characterized by the progressive loss of memory and cognitive functions. In mammals, the hippocampus is involved in the process of learning and memory, and it has been reported to exhibits amyloid-dependent structural and functional degradation in the early stage of AD. Therefore, hippocampus is an extremely important region for understanding the mechanisms of memory encoding and recall impairment in Alzheimer's disease. Recent studies have demonstrated that AD patients and animal models exhibit hyperactivity of hippocampal excitatory neurons caused by GABAergic inhibitory interneurons dysfunction and reduced gamma oscillations. Parvalbumin interneurons (PVINs), a type of GABAergic inhibitory interneuron, play a crucial role in generating gamma oscillations and regulating sleep states. However, the roles of PVINs in the early hippocampal pathogenesis progression of AD remain unknown. Based on previous findings, we hypothesis that PVINs dysfunction leads to excitatory and inhibitory (E/I) imbalance, pyramidal neurons hyperactivity, and amyloid plaque accumulation in the dorsal hippocampus during the pathogenesis of AD. Here we used *in vivo* longitudinal imaging method to examine amyloid plaque, blood vessel, and neuronal structural changes in the dorsal hippocampus of AD mouse from early to late stages of disease. We found young 5XFAD mouse hippocampal PVINs exhibit structural and functional damage, and show early sleep disturbance, followed by progressive plaque accumulation, vascular degeneration, and excitatory neuronal damage in the dorsal hippocampus, leading to later cognitive impairment. These findings would be important for uncovering the fundamental role of dorsal hippocampal PVINs in the progression of AD and exploring the potential therapeutic intervention for prevention and treatment of AD.

Disclosures: W. Xie: None. **C.S. Lai:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.05/B93

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

Support: NIH Grant R01AG061785-A1

Title: Altered Clock Gene Expression in Parvalbumin Interneurons in an Alzheimer's Disease Model

Authors: *M.-M. COOPER[1], E. D. ROBERSON[2], K. L. GAMBLE[3], R. M. COWELL[4]; [1]Neurol., Univ. of Alabama at Birmingham (UAB), Birmingham, AL; [2]Neurol., Univ. of Alabama, Birmingham, Birmingham, AL; [3]Psychiatry, Univ. of Alabama at Birmingham, Birmingham, AL; [4]Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Alzheimer's disease (AD) features subclinical epileptiform activity predominantly at night, during the inactive phase of the circadian rhythm. Mouse models of AD also have epileptiform activity during the inactive phase. Parvalbumin (PV) interneurons are the most abundant interneuron type in the hippocampus and cortex and likely contribute to hyperexcitability. Because epileptiform activity in AD follows a clear circadian rhythm of expression (higher during the inactive phase), we hypothesized that clock dysfunction in PV interneurons of the hippocampus and cortex contributes to AD-related hyperexcitability. To begin testing this hypothesis we asked if there are alterations in the transcription of core clock genes in PV interneurons in the hippocampus and cortex of the hAPPJ20 mouse model of AD. Mice were entrained for two weeks using controlled lighting, released into constant darkness for 2 days, then brains were collected every 4 hours at 6-time points. RNAscope was used to visualize clock genes Rora, Per1, Nr1d1, and clock-controlled gene Scn1a within the PV cells in the hippocampus and cortex.We found altered circadian rhythms of core clock gene expression in both cortical and hippocampal PV interneurons of our AD mouse model compared to controls. Future studies include the analysis of additional cell types of interest (i.e. Somatostatin) and measure behaviors associated with clock gene rhythm dysfunction across circadian time.

Disclosures: M. Cooper: None. **E.D. Roberson:** A. Employment/Salary (full or part-time):; University of Alabama at Birmingham. 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.; Grants from NIH, Bluefield Project to Cure FTD, Alzheimer's Drug Discovery Foundation, site PI for clinical trials with Eisai and Lilly.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Owner of IP related to tau, royalties on mouse model licensed to Genentech. F. Consulting Fees (e.g., advisory boards); Member of SAB for AGTC, Member of DMC for Lilly, Member of Editorial Board for SfN. **K.L. Gamble:** None. **R.M. Cowell:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.06/B94

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

Support: NIH-NIDS R01NS065808
NIH-NIDS R01NS127403
Rosenau Family Research Foundation
European Leukodystrophies Association

Title: Haploinsufficiency of the Lysosomal Enzyme Galactosylceramidase contributes to an accelerated manifestation of Alzheimer Disease

Authors: *D. ZELADA[1], N. SALDIVIA[2], J. WHITEHAIR[2], S. SAMANO[2], S. RAJESH[2], O. LAZAROV[3], E. R. BONGARZONE[2];
[1]Anat. and Cell Biol., Univ. of Illinois at Chicago, Chicago, IL; [2]Univ. of Illinois at Chicago, Chicago, IL; [3]Anat. and Cell Biol., The Univ. of Illinois at Chicago, Chicago, IL

Abstract: There are interesting new insights about the mechanisms leading to adult-onset neurodegenerative diseases, especially the evidence coming from Lysosomal Storage Diseases (LSD). LSDs are inherited metabolic disorders affecting more commonly to infants by the dysfunction of lysosomal enzymes that leads to the accumulation of toxic substrates. In this regard, the dogma is that carriers for mutations in LSD-related enzymes live normally and have no alterations in the disease burden. However, in this work, we are challenging the hypothesis that decreased activity of lysosomal enzymes contribute to the vulnerability of the adult brain to neurodegeneration. One of the potential candidates is the lysosomal enzyme Galactosylceramidase (GALC), involved in Krabbe Disease (KD), where it has been reported the misfolding and aggregation of α-synuclein. Thus, in this work we have generated a GALC haploinsufficiency 5x Familiar Alzheimer Disease (5xFAD) mouse model and evaluated the impact on neuropathological manifestations. For this, we performed Novel Object Recognition (NOR) test at different time points, immunopathological analyses of neuroinflammation, astrogliosis, microgliosis, Aβ deposition, and biochemical analyses of brain tissues. Our data provide novel evidence associating GALC as a factor promoting the early manifestation of adult-onset neurodegenerative diseases, such AD.

Disclosures: D. Zelada: None. **N. Saldivia:** None. **J. Whitehair:** None. **S. Samano:** None. **S. Rajesh:** None. **O. Lazarov:** None. **E.R. Bongarzone:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.07/B95

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

Support: NIH R01AA025718
Fondecyt 1221080
PhD ANID Fellowship 21211228

Title: Changes in Excitatory Synaptic Neurotransmission in the Basolateral Amygdala from APP/PS1 Alzheimer's Disease Mice

Authors: J. GONZÁLEZ-SANMIGUEL, L. S. SAN MARTIN, N. RIFFO-LEPE, P. SAAVEDRA SIEYES, I. MEZA VARGAS, D. HERNANDEZ CASTILLO, L. G. AGUAYO; Univ. de Concepción, Concepción, Chile

Abstract: It is becoming recognized that Alzheimer's disease (AD), a progressive neurodegenerative disorder, presents early non-cognitive impairments. Furthermore, recent experimental evidence shows several changes in synaptic neurotransmission in limbic circuits of AD animal models, occurring prior to the appearance of amyloid plaques. The basolateral amygdala (BLA), a brain region crucial for emotional processing, shows early alterations in both human and AD animal model studies. However, there is limited information on possible synaptic alterations in the BLA during AD progression. Therefore, we evaluated the presence of AD pathology in 6-month-old APP/PS1 AD mice, an age corresponding to the early stage of the disease in this mice model. Immunohistochemical analysis showed the presence of intracellular amyloid beta (iAβ), but no extracellular plaques in coronal BLA slices. Western blot experiments to study synaptic proteins in the BLA showed a significant increase in PSD95 in the APP/PS1 mice (WT: 0.43 ± 0.08 AU; APP/PS1: 0.7 ± 0.03 AU). Subsequently, excitatory and inhibitory synaptic activities were studied using the patch clamp technique. The results showed a significant increase in AMPAR-mediated mEPSCs charge transfer in the APP/PS1 mice (WT: 52.4 ± 4 pA·ms; APP/PS1: 93.1 ± 17 pA·ms). Consequently, AMPA-evoked current density in dissociated neurons of the BLA also showed an increase in APP/PS1 (9.03 ± 0.9 pA/pF) compared to WT (6 ± 1 pA/pF). Conversely, GABAAR-mediated mIPSCs charge transfer decrease significantly in the APP/PS1 mice. For instance, the transferred charge in WT and AD mice was 105 ± 8 pA·ms and 133 ± 9 pA·ms, respectively. To evaluate postsynaptic alterations in the synapsis, AMPA/NMDA ratio was measured. The results show a decreasing trend in this ratio in APP/PS1 animals. Intrinsic membrane properties examined by current-clamp recordings showed a reduction in action potentials (WT: 8 ± 0.5; APP/PS1: 6.3 ± 0.5 during a 250 pA pulse) and membrane resistance (WT: 124 ± 6.8 MΩ; APP/PS1: 104 ± 6.9 MΩ) in APP/PS1 mice. Overall, these findings suggest that elevated iAβ levels in the BLA of 6-month-old APP/PS1 mice produce an alteration in the excitatory/inhibitory balance together with a reduced action potential firing, suggestive of compensatory mechanisms.

Disclosures: J. González-Sanmiguel: None. **L.S. San Martin:** None. **N. Riffo-Lepe:** None. **P. Saavedra Sieyes:** None. **I. Meza Vargas:** None. **D. Hernandez Castillo:** None. **L.G. Aguayo:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer’s Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.08/B96

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

Support: AARF-22-973747

Title: Synaptic plasticity and memory impairments caused by extracellular Aβ and Tau oligomers are dependent upon presynaptic amyloid precursor protein.

Authors: *E. ACQUARONE[1], H. ZHANG[1], A. STANISZEWSKI[1], L. D'ADAMIO[2], D. PUZZO[3], A. F. TEICH[1,4], O. ARANCIO[1];
[1]Columbia Univ. Med. Center: Columbia Univ. Irving Med. Ctr., New York, NY; [2]Rurgers, Newark, NJ; [3]Dept Biomed. and Biotechnological Sci. Section Of Physiol., Univ. of Catania, Catania, Italy; [4]Dept. of Neurol., Columbia Univ. Med. Ctr., New York, NY

Abstract: Recent literature shows that Amyloid Precursor Protein (APP) is necessary for the entrance of soluble oligomeric forms of Aß and Tau into neurons. Moreover, in absence of APP, extracellular Aß- and tau-oligomers no longer impair memory and its synaptic surrogate, long-term potentiation (LTP). Synapses include pre- and post-synaptic compartments. However, the relative role of pre- vs. post-synaptic APP at the CA3-CA1 hippocampal synapse in the Aß- and tau-oligomer-induced damage of memory and LTP is not known. Using a combination of gene editing, electrophysiological, optogenetic, behavioral and biochemical techniques, we dissected the relative role of pre- vs. post-synaptic APP at the CA3-CA1 hippocampal synapse in the Aβ- and tau-induced damage of memory and LTP. We found that pre- (but not post-) synaptic APP deletion occluded both Aβ and tau oligomer induced LTP and memory defects. Consisting with these findings, Aβ and Tau oligomer reduced neurotransmitter vesicle availability during tetanic stimulation, an effect that was blocked and mimicked by conditional inactivation of APP in mouse pre-synaptic CA3 excitatory neurons, but not CA1 neurons. Moreover, Aβ- and Tau oligomers increased the refilling rate of the readily releasable pool (RRP), an effect that was blocked and mimicked by inactivation of APP in mouse pre- (but not post-) synaptic CA3 excitatory neurons. Interestingly, inactivation of APP in mouse pre-synaptic CA3 excitatory neurons affected refilling of the RRP through calcium-dependent mechanisms, and consisting with this finding intracellular calcium homeostasis was disrupted both in basal conditions and after activity in APP knock-out mice. These data support the view that Aß and tau oligomers affect synaptic function and memory through pre-synaptic APP and dysregulation of calcium homeostasis.

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Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.09/B97

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

Title: Physiological effect of pathological tau at the hippocampal excitatory synapse

Authors: *E. LEGGETT[1], R. MCQUISTON[2];
[1]Virginia Commonwealth Univ. Dept. of Anat. and Neurobio., Richmond, VA; [2]Dept Anat/Neurobiol, Virginia Commonwealth Univ., Richmond, VA

Abstract: Alzheimer's disease is an incurable neurodegenerative disease marked by memory impairment and personality changes. It is the sixth leading cause of death in the United States. Alzheimer's disease is accompanied by a progressive accumulation of oligomeric phosphorylated forms of microtubule-associated protein tau. Two of the first affected cortical regions are the entorhinal cortex and its downstream target the hippocampus, particularly the CA1 region. The accumulation of oligomeric phosphorylated tau has been correlated with cell death and cognitive decline. This can be modeled by expressing human tau mutants found in frontotemporal dementia (FTLD) patients, which are more efficiently phosphorylated relative to wild type variants. In particular, a P301L/S320F double mutant of tau has been shown to rapidly hyperphosphorylate in a mouse model (Koller et al 2019, Strang et al 2018). In our lab, in as early as 3 weeks post injection, intracranial hippocampal injection of an adeno-associated virus (AAV) carrying the coding sequence for P301L/S320F mutant tau resulted in the expression of hyperphoshorylated and misfolded tau detected through immunoreactivity to the phosphorylation specific antibodies CP13 and PHF-1 as well as the conformation specific antibody MC1. To examine the physiological effect of this mutant protein, we injected ventral hippocampal CA1 of male and female CAMKIIα-cre mice with an AAV encoding the double mutant P301L/S320 tau controlled by a FLEx switch. Using patch clamp electrophysiology, we investigated the effect of P301L/S320F tau on the electrophysiological and synaptic properties of CA1 pyramidal neurons in mouse hippocampal slices. We measured both electrophysiological responses to current injections and postsynaptic current responses to trains of stimuli delivered to presynaptic axons by a bipolar stimulating electrode. We also determined the AMPA to NMDA ratio of these synaptic connections. The presence of the phosphorylated tau was confirmed by immunofluorescence. These experiments will help understand the autonomous effect that hyperphosphorylated tau has on hippocampal CA1 pyramidal neurons and their vulnerability at early stages of dementia.

Disclosures: E. Leggett: None. **R. McQuiston:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.10/B98

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

Support: Kuwait University grant/MR01/21

Title: Role of oxidative stress and hyperphosphorylation of tau-396 in the loss of synaptic proteins as an early pathogenesis of sporadic Alzheimer's disease

Authors: *M. A. ANSARI[1], M. S. RAO[2];
[1]Kuwait Univ., Kuwait, Kuwait; [2]Anat., Col. of Med., Kuwait Univ., Jabriya, Kuwait

Abstract: Although the precise etiology of Alzheimer's disease (AD) remains to be elucidated, several studies have supported the idea that synaptic dysfunction/loss, in key brain regions, may be a pivotal event leading to dementia. Our previous studies on AD human samples have revealed a significant decline in synaptic number and their associated proteins in the hippocampus during AD progression and the loss of synaptic proteins in the hippocampus was strongly correlated with oxidative stress markers. Present study was designed to test whether or not levels of synaptic proteins are altered in the hippocampal synaptosomes in the early stage of dementia. To address this, we used impaired brain insulin signaling model in adult male Wistar rats. In the present study, early dementia was induced in adult male Wistar rat with intraperitoneal (IP, 50 mg/kg, n=20, 10 for each 3 weeks and 6 weeks group) and intracerebroventricular (ICV,) infusion of streptozotocin (STZ, 3mg/kg, n=20, 10 for each 3 weeks and 6 weeks group). Rats in STZ injected and age matched control group (n=20, 10 for each 3 weeks and 6 weeks group) were sacrificed 3 or 6 weeks after STZ injection. Cognitive behavior of the rats in all groups was assessed using Morris water maze (MWM) tests, a week before sacrifice (during 3rd, and 6^{th} week). Hippocampi were dissected, synaptosomes were prepared and were examined for oxidative stress markers, glycogen synthase kinase-3α/β (GSK-3α/β), hyperphosphorylation of tau-396 (p-Tau396), pre- and post-synaptic proteins. Data were analyzed with One-way/Two-way ANOVA followed by Bonferroni's multiple comparison test. The results showed compromised brain insulin function impaired rat's cognitive status significantly ($p<0.05$), which was significantly correlated with increased oxidative stress ($p<0.05$), GSK-3α/β ($p<0.05$), p-Tau($p<0.05$) and declined levels of pre- and post-synaptic proteins ($p<0.05$). Biochemical changes in the hippocampus were significantly correlated with the impaired cognition of the animal($p<0.05$). Our data implicates the oxidative stress into pathophysiologic changes during early sAD progression, which also suggests antioxidant therapy should be initiated at earliest cognitive impairment noticed in diabetes. The hippocampus may be much sensitive for the impaired insulin function related changes, and future therapeutic interventions should concentrate on the progression of dementia in diabetes.

Disclosures: M.A. Ansari: None. **M.S. Rao:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.11/B99

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

Support: The Garrison Family Foundation and Center of Excellence for Translational Neuroscience and Therapeutics, TTUHSC

Title: Cerebellin1 alleviates cognitive deficits in a mouse model of Alzheimer's disease (J20 mice)

Authors: *Y. CHEN[1,2], X. YIN[1], T. KIRITOSHI[3], P. D. PRESTO[3], M. MAZZITELLI[3], M. MANCZAK[1,4], V. NEUGEBAUER[1,2,4];
[1]Garrison Inst. on Aging, Texas Technol. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Department of Pharmacology and Neuroscience, Texas Tech University Health Science Center, Lubbock, TX; [3]Dept. of Pharmacol. and Neurosci., Texas Technol. Univ. Hlth. Sci. Ctr., Lubbock, TX; [4]Center of Excellence for Translational Neuroscience and Therapeutics, Texas Tech University Health Science Center, Lubbock, TX

Abstract: The aim of this study is to investigate the roles of cerebellin1 (Cbln1) in cognitive functioning at the early stages of Alzheimer's disease (AD) pathology in a mouse model (J20 mice). As a secreted synaptic organizer in the central nervous system, Cbln1 connects presynaptic neurexins to postsynaptic delta glutamate receptors, GluD1/GluD2, to form the trans-synaptic neurexin-Cbln1-GluD1/2 complex. These complexes are thought to be critical for regulating synapse properties. However, it remains unclear if Cbln1 has any impact on the neuronal network dysfunction observed in AD pathology, especially at the early stages. In this study, we chose 8-month-old male J20 AD mice as our animal model for early stage of AD, because J20 mice show amyloid-beta deposits, beginning plaque formation, and cognitive behavioral deficits by this age. We performed Western blot analysis in hippocampus tissues isolated from wild type (WT) and J20 AD mice and found that expression of Cbln1 significantly decreased in J20 AD mice compared with WT mice. We thus hypothesized that restoring Cbln1 levels might ameliorate cognitive decline observed in J20 AD mice. To do so, we stereotaxically administered recombinant human Cbln1 or vehicle (0.9% NaCl) into the lateral ventricles of J20 mice and age- and sex-matched WT mice. Subsequent behavioral assessments, including the Morris Water Maze (MWM) and Novel Object Recognition Task (NORT), revealed significant learning and memory deficits in vehicle-treated J20 mice compared with vehicle-treated WT mice and Cbln1-treated J20 mice, suggesting that Cbln1 administration alleviated cognitive deficits of J20 mice. Electrophysiological recordings of long-term potentiation (LTP) in hippocampal slices from Cbln1-treated J20 mice and vehicle-treated WT and J20 mice showed that Cbln1 largely restored LTP in J20 mice. Together, these results suggest that Cbln1 can alleviate cognitive deficits and restore neuroplasticity in 8-month-old J20 AD mice.

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Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.12/B100

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

Support: Tulane University start-up funds and an administrative supplement GM109036 (EEC)
Tulane Center for Translational Research in Infection & Inflammation
NextGen Sequencing Core and Tulane Proteomics Core

Title: Elucidating the Contributions of Neuronal-Specific miR34a Upregulation in Alzheimer's Disease Pathogenesis: A Comprehensive Assessment of a Novel Inducible Neurodegenerative Animal Model

Authors: *R. FREITAS[1], I. PURSELL[2], N. BARAHONA[1], L. WEGROWSKI[1], E. B. ENGLER-CHIURAZZI[2];
[1]Tulane Univ., NEW ORLEANS, LA; [2]Neurosurg., Tulane Univ., New Orleans, LA

Abstract: MicroRNAs (miRNAs), which are small RNA sequences that influence protein synthesis, are implicated in the mechanisms of neurodegeneration. Specifically, microRNA-34a (miR-34a) is an essential modulator of a variety of genes linked to neurodegenerative conditions, including those involved in protein aggregation and synaptic function. We developed a global Tet-inducible miR-34a overexpressing mouse line in which cognitive deficits, altered amyloid and tau protein processing, and synaptic reorganization were noted. To address cell-specificity of miR34a effects, we also generated a CaMKIIα driven, excitatory neuron-specific Tet-inducible miR-34a overexpressing mouse model. Male and female miR-34a+/- mice aged 28-46 weeks were treated with water or Doxycycline 2mg/mL (Doxy) to induce miR-34a overexpression for 30 days cognitive and neurobiological consequences were assessed. In this pilot study, we assessed the expression of predicted miR-34a target genes and associated proteins (e.g. SIRT1, MMDAR2B). A subset of mice underwent bulk RNA sequencing and proteomics analysis in one brain hemisphere to identify novel miR-34a targets. At 30 days of miR-34a overexpression, we observed trends towards reduced levels of miR-34a target genes (NMDAR2B, SHANK3) in the hippocampus of mice. However, these findings were non-significant, likely attributed to the limited power or insufficient exposure duration. No cognitive differences were observed at 30 days of exposure to miR34a overexpression. Hippocampus and cortex were isolated for miRNA analysis and indicated region specific changes. Whole brain hemisphere bulk RNA sequencing of Doxy-treated animals revealed upregulation of growth hormone (Gh) and prolactin (Prl) genes and downregulation of vasopressin (Avp) and dopamine receptor D1 (Drd1) compared to

control. Proteomic analyses are currently underway; our primary focus is on the alterations in glutamatergic signaling proteins due to miR-34a overexpression. Specifically, we are examining the effects on critical components such as NMDAR2B, GLUR7, and other pivotal glutamatergic receptors that play essential roles in synaptic function. Further exploration is warranted to elucidate the contributions of other neural or peripheral cell types to AD phenotype precipitated by global miR-34a overexpression. The cell-specific design of our model offers critical insights into the role of miR-34a in AD pathology. These observations enhance our comprehension of the intricate, polygenic mechanisms that underlie neurodegeneration in AD, potentially unveiling new microRNA-focused therapeutic targets.

Disclosures: R. Freitas: None. **I. Pursell:** None. **N. Barahona:** None. **L. Wegrowski:** None. **E.B. Engler-Chiurazzi:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.13/B101

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

Support: ARUK-PPG2021B-012
PharmAlliance PARCDT

Title: Positive allosteric modulation of extrasynaptic δ-GABAA receptors alleviate symptoms of Alzheimer's disease

Authors: *A. CHAN[1], W. ZHANG[1], C. ARBER[2], S. WRAY[2], O. POPA[3], J. R. ATACK[3], A. B. ALI[1];
[1]Sch. of Pharm., Univ. Col. London, London, United Kingdom; [2]Inst. of Neurol., Univ. Col. London, London, United Kingdom; [3]Cardiff Univ., Cardiff, United Kingdom

Abstract: Alzheimer's disease (AD) is the most prevalent dementia, a global health concern that affects over 55 million people worldwide. AD is associated with gradual memory loss and anxiety that affects ~70% of AD patients. There is currently a gap in our knowledge of the pathobiology of anxiety associated AD; furthermore, we lack effective medication that has been rationally designed to treat these symptoms without serious side-effects. AD-associated toxic amyloid-beta accumulation causes synaptic dysfunction correlated with destruction of selective parvalbumin (PV)- expressing interneurons that co-express extrasynaptic δ-subunit- containing $GABA_A$ receptors (δ-$GABA_A$Rs), that play a role in mood disorders. We hypothesize that alteration of δ-$GABA_A$Rs could correlate with anxiety in AD and modulating this receptor could have potential in developing novel treatments for AD. To test this hypothesis, behavioural studies, combined with neurochemistry and cell biology, were performed using a familial AD mouse model ($APP^{NL\text{-}F/NL\text{-}F}$) age-matched (12-16 months) to wild-type (WT) control mice. *In-*

vitro human-induced pluripotent stem cell culture (hiPSCs) models generated from familial AD patients carrying *APP* mutations, and their isogenic controls were also utilized in this study. Neurochemistry experiments revealed a layer-specific expression of δ-$GABA_A$Rs in the hippocampal CA3 region, compared to the CA1 stratum in both genotypes. Z-stack confocal microscopy revealed a significant reduction in the δ-$GABA_A$Rs colocalised with PV interneurons throughout hippocampal subregions in $APP^{NL\text{-}F/NL\text{-}F}$ mice compared to age-matched WT mice. Interestingly, δ-$GABA_A$Rs were not colocalised with CAMKIIα-expressing pyramidal neurons. These observations were also evidenced in hiPSCs models. *In-vivo* dosing (5 days) with either a novel positive allosteric modulator (PAM) of δ-$GABA_A$Rs, MDI-0117289, identified by Professor Atack (Cardiff University), or vehicle, using cohorts of $APP^{NL\text{-}F/NL\text{-}F}$ mice at 12-16 months was followed by behavioural studies consisting of a light/dark chamber paradigm and T-maze paradigm to measure anxiety and working memory. These experiments revealed that MDI-0117289 treatment decreased anxiety and improved cognitive decline which was correlated with a "normalisation" of the expression of δ-$GABA_A$Rs compared to the vehicle treated group. These data suggest that extrasynaptic δ-$GABA_A$Rs are selectively expressed in neurons in mouse and human dementia models, and that positive allosteric modulation of these receptors has a promising potential in developing a novel targeted therapy for alleviating cognitive decline and anxiety in AD.

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Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.14/B102

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

Support: CSIC I+D 2022
ANII-Fondo Clemente Estable

Title: Time-course changes in glutamatergic and melanin-concentrating hormone systems in the streptozotocin-induced sporadic Alzheimer's disease model in male rats

Authors: S. NIÑO-RIVERO[1], M. DE CEGLIA[2], J. URBANAVICIUS[3], A. GAVITO COLLADO[4], F. RODRÍGUEZ DE FONSECA[5], ***P. LAGOS**[1];
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Abstract: Alzheimer's disease (AD has currently limited treatment options. Development of new therapeutic strategies is thus fundamental. Hippocampal glutamatergic transmission has long been related to the development of AD. Although prior AD studies have extensively characterized several other neurotransmitter systems that project to the hippocampus, the hypothalamic melanin-concentrating hormone (MCH) system, has been overlooked despite the dense MCH fibers presence at the hippocampus. In addition, MCH has been reported to elevate NMDAR levels and to increase synaptic efficacy. Thus, in the current work we sought to explore the relationship of these neurotransmitter systems in an animal model of sporadic AD induced by the intracerebroventricular administration of streptozotocin (STZ). Our group has previously determined an early phase occurring 15 to 30 days post-STZ injection, characterized by anatomical changes in neuronal and glia number and density at the cortex and hippocampus, with no measurable memory impairments. A late phase begins 90 days post-STZ with significant memory deficits. We administered STZ (3mg/kg) or artificial cerebrospinal fluid (aCSF) to adult male rats and sacrificed them at 15, 30, 60, 90, and 120 days (n=8-10/group). NMDAR subunits, prepro-MCH and MCHR-1 receptors were analyzed in the hippocampus and hypothalamus by biochemical and molecular techniques. We found that at the hippocampus NMDAR-2A levels were significantly increased in STZ-15 and STZ-60 groups, whereas *Grin2A* mRNA levels were increased in STZ-30. NMDAR-1 and 2B levels did not change in any STZ groups. Although at the hippocampus, MCHR-1 number (present at primary cilia) and MCHR-1 levels did not change, interestingly *prepro-MCH* mRNA levels showed a significant decrease whereas *MCHR-1* mRNA levels increased at STZ-30. At the hypothalamus, MCHR-1 levels showed a significant increase at STZ-30, although CSF-MCH levels did not show modifications. No modifications of NMDAR subunits were observed at the hypothalamus. All comparisons are between STZ to aCSF; all data was subject to either student t-test or ANOVA; results were significant at $p<0.05$. Our results show significant anatomical changes at MCH system at pre and post-synaptic levels at the early phase. In addition, modifications at NMDAR2A, an important subunit related to the sensibility of NMDA channel, were also detected. Together, these findings suggest a new avenue of treatment focuses on MCH system associated with the known classical glutamatergic system and its NMDA receptors.

Disclosures: S. Niño-Rivero: None. **M. de Ceglia:** None. **J. Urbanavicius:** None. **A. Gavito Collado:** None. **F. Rodríguez De Fonseca:** None. **P. Lagos:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.15/B103

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

Support: NIH RF1AG072727
NIH RF1AG069378

Title: Decoding Noradrenergic Dysfunction in the App^{NL-G-F} Mouse Model of Alzheimer's Disease

Authors: *N. KILIÇ[1], H. KAUR[2], C. K. COMBS[3];
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Abstract: Our understanding of Alzheimer's disease (AD) has evolved significantly over the years, yet many mysteries persist, particularly regarding the early changes that precipitate neuronal death. Among these, the locus coeruleus (LC), with its dense population of noradrenergic neurons, remains a point of interest based on its early degeneration in AD. However, the precise mechanism of LC cell loss and resulting consequences on disease remain unclear. To better understand LC changes during disease, we compared six-month-old male and female C57BL/6wild-type mice to the App^{NL-G-F} knock-in model of AD (n=6). Immunostaining for tyrosine hydroxylase (TH), as the rate-limiting enzyme for norepinephrine synthesis, was used to quantify cell loss in the LC. As a relevant efferent output of the LC, we quantified norepinephrine levels in the hippocampus and compared this, via western blot, to levels of metabolic enzymes TH, dopamine beta-hydroxylase, monoamine oxidase A (MAO-A), catechol-O-methyltransferase(COMT), and monoamine oxidase-B (MAO-B). We also evaluated overall presynaptic and postsynaptic compartment integrity by quantifying levels of synaptophysin and PSD95, respectively. Furthermore, we assessed compensatory changes in noradrenergic receptor (AR)levels. As anticipated, we observed a significant reduction in hippocampal norepinephrine levels in both female and male App^{NL-G-F} mice compared to wild-type controls. Surprisingly, this decrease did not correlate with changes in TH immunoreactivity in the LC, suggesting that cell death may not be the primary cause of reduced norepinephrine levels. To investigate the possibility of altered norepinephrine synthesis or turnover contributing to the decrease in norepinephrine levels, we examined levels of metabolic enzymes and observed an increase in pTH/TH in male App^{NL-G-F} mice, a decrease in MAO-B levels in female App^{NL-G-F} mice, and an increase in MAO-A levels in both sexes of App^{NL-G-F} mice compared to wild type controls. As a possible consequence of norepinephrine deficiency, we observed increased α-1B AR levels in male App^{NL-G-F} mice, a decrease in α-2C AR levels in female App^{NL-G-F} mice, and elevated levels of β-2 AR in male and female App^{NL-G-F} mice compared to wild-type controls. These findings indicate a common modulation of β-2 AR and MAO-A levels in both sexes of App^{NL-G-F} mice, not associated with significant cell death or synaptic loss. This suggests a potential selective disruption in adrenergic signaling, which may represent an early phenotype change during disease progression, preceding or contributing to eventual neuron and synaptic loss.

Disclosures: N. Kiliç: None. **H. Kaur:** None. **C.K. Combs:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer's Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.16/B104

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

Title: Reduction of Ach release via impaired acetylcholine metabolic cycle in the hippocampus of hippocampal cholinergic neurostimulating peptide precursor protein KO mice

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Abstract: [Objective] Hippocampal Cholinergic Neuro-stimulating Peptide (HCNP) was originally discovered from soluble fraction of rat hippocampus, which induces acetylcholine (Ach) synthesis in the medial septal nucleus. HCNP is aligned at the N-terminal region of 21-kD HCNP precursor protein (HCNP-pp), a multifunctional protein, also known as Raf kinase inhibitory protein (RKIP) and phosphatidylethanolamine-binding protein 1 (PEBP1). We reported that in microdialysis Ach concentration was decreased in the hippocampus of HCNP-pp conditional knockout (cKO). Here, to clarify mechanism of Ach decrease we examined Ach release and choline metabolic function. **[Methods]** After incubation with [^{3}H]choline, hippocampal slices were placed in a small vessel of ultra-mini superfusion system, and perfused by artificial cerebrospinal fluid, containing 136.2 mM Na^+, 3 mM K^+, 2.4 mM Ca^{2+} and 134.2 mM Cl^-, at a rate of 0.8 ml/min. After each electrical stimulation, the perfused medium was sampled every a minute to detect [^{3}H] ACh release. We also calculated the ability of choline incorporation and synthesis ability of Ach by measure of [^{3}H] choline and [^{3}H] Ach in slices by reverse-phase high-performance liquid chromatography. **[Results]** No significant difference was shown in [^{3}H] efflux by single stimulation between 6-month-old HCNP-pp cKO and wild type (WT) mice. However, the [^{3}H] efflux by repetitive stimulation at 5-min intervals rapidly decreased in HCNP-pp cKO compared to WT. The similar pattern of decay was observed in WT treated with vesamicol, a blocker of vesicular Ach transporter (VAchT). [^{3}H] accumulation in slices, uptake quantity of [^{3}H] choline and [^{3}H] Ach concentration in HCNP-pp cKO was lower than that in WT. The same tends to be shown over 12-month-old mice. These results suggest that Ach release was reduced in HCNP-pp cKO thorough CHT1, ChAT and VAchT dysfunction compared to WT. **[Conclusion]** The impairment of Ach metabolic cycle may be involved in reduction of Ach release in the hippocampus of HCNP-pp cKO mice.

Disclosures: I. Nagai-Arakawa: None. **I. Muramatsu:** None. **N. Tajiri:** None. **N. Matsukawa:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer’s Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.17/B105

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

Support: Boettcher Foundation
BrightFocus Foundation
NIH/NCATS Colorado CTSA Grant UL1 TR002535
NIA Grant R03AG072102
Colorado State University

Title: Selective cholinergic activation prevents hippocampal hyperexcitability, memory loss, and the in vivo growth of amyloid plaques in Alzheimer’s disease

Authors: *E. BLACK, R. LEE, S. KIM;
Colorado State Univ., Fort Collins, CO

Abstract: Alzheimer’s disease (AD) is the most common form of dementia with no known cause and cure. Studies suggest that one of the main causes of AD is disruptions in synaptic activity of GABAergic inhibitory interneurons by beta-amyloid peptide (Aβ). This in turn decreases inhibitory activity to increase excitation in pyramidal excitatory neurons in the hippocampus, resulting in network hyperexcitability. Hyperexcitability in the hippocampal network also promotes Aβ secretion and accumulation, leading to the formation of amyloid plaques, a central pathology of AD. This suggests that the Aβ-induced reduction of hippocampal inhibition is a crucial trigger for the development of AD. Therefore, enhancing hippocampal interneuron activity is thought to be neuroprotective against AD. We thus hypothesize that Aβ-induced hippocampal hyperexcitation promotes the in vivo rapid growth of amyloid plaques, which can be reversed by increasing hippocampal inhibition. To activate hippocampal inhibition, we injected drugs to stimulate α7- and α4β2-nicotinic acetylcholine receptors (nAChRs) into 5-month-old amyloid pathology model (5XFAD) mice. hippocampal sections from these mice were stained with Thioflavin S to visualize amyloid plaques. We found that in vivo co-stimulation of α7- and α4β2-nAChRs significantly reduced the total area and average size of amyloid plaques in the 5XFAD hippocampus when compared to the control hippocampus. This suggests that co-activation of these two receptors significantly reduces the growth of amyloid plaques in 5XFAD mice by preventing hyperexcitation in hippocampal pyramidal cells.

Disclosures: E. Black: None. **R. Lee:** None. **S. Kim:** None.

Poster

PSTR327: Cognitive and Synaptic Dysfunction in Alzheimer’s Disease: New Interventions and Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR327.18/B106

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

Support: Boettcher Foundation
Bright Focus Foundation

NIH/NCATS Colorado CTSA Grant UL1 TR002535
NIA grant 1R03AG072102

Title: Co-activation of selective nicotinic acetylcholine receptors improves hippocampal rhythmic activity and memory in Alzheimer's disease

Authors: *R. LEE, E. BLACK, S. KIM;
Colorado State Univ., Fort Collins, CO

Abstract: Different subtypes of GABAergic inhibitory interneurons produce hippocampal oscillations where reduced activity in these interneurons is linked to lower oscillatory activity and memory loss in AD. In the early stages of AD, beta-amyloid peptide (Aβ) is linked to decreased hippocampal oscillations due to decreased GABAergic inhibition, resulting in cognitive impairment, the mechanism however is unknown. A prominent AD pathology in the human brain is the loss of cholinergic neurons and nicotinic acetylcholine receptor (nAChR) expression. Our findings show that co-activating the subtypes α7- and α4β2-nAChRs in vivo improves memory in an AD mouse model. We hypothesize that Aβ reduces hippocampal GABAergic activity by selectively inhibiting α7- and α4β2-nAChRs, resulting in hippocampal oscillation disruption and memory loss in AD, and that selective coactivation reverses the Aβ-induced pathological effects. The AD mouse model, 5XFAD transgenic mice, with wild type (WT) littermates treated intraperitoneally with α7- and α4β2-nAChR agonists 1 μM PNU-282987 and 2 μM RJR-2403 Oxalate respectively at concentrations of 5mg/ml for 7 days. We compare both mice models with same volume of 0.9% saline as control. We performed stereotaxic surgery to insert electrodes into CA1 of hippocampus to measure local field potential of theta and gamma oscillations. At control conditions we found that 5XFAD and WT mice had similar power spectrum density (PSD). After consolidation there was definite decrease in PSD for 5XFAD mice. Then we found that with co-stimulation of nAChRs we can rescue the PSD. We also performed fear conditioning to see if memory consolidation increases with dual injection of the agonists. We observed that with control conditions 5XFAD has clear deficit in contextual memory which is then successfully rescued by co-activation.

Disclosures: R. Lee: None. **E. Black:** None. **S. Kim:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.01/B107

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

Support: ASU Edson Initiative Seed Grant

Title: Glyphosate exposure exacerbates neuroinflammation and Alzheimer's disease-like pathology despite a 6-month recovery in NonTg and 3xTg-AD mice

Authors: *S. BARTHOLOMEW[1,2], W. WINSLOW[1], R. SHARMA[3,4], K. PATHAK[3,4], S. TALLINO[1,2], J. M. JUDD[1], H. LEON[1], P. PIRROTTE[3,4], R. VELAZQUEZ, Jr.[1,2]; [1]Neurodegenerative Dis. Res. Ctr., Arizona State Univ., Tempe, AZ; [2]School of Life Sciences, Arizona State University, Tempe, AZ; [3]TGen, Phoenix, AZ; [4]Mass Spectrometry Shared Resources (IMS-SR), City of Hope Comprehensive Cancer Center, Durante, CA

Abstract: Glyphosate use in the United States (US) has increased each year since the introduction of glyphosate-tolerant crops in 1996, yet little is known about its effects on the brain. Recent reports have shown that ~90% of adults and children tested in a US show traces of glyphosate, and its major metabolite, aminomethylphosphonic acid, in urine, suggesting chronic exposure. Most studies on glyphosate exposure have focused on links to cancer and ailments to peripheral body organs, including the liver and kidneys. Our lab recently found that C57BL/6J mice dosed with glyphosate for 14 days show glyphosate and aminomethylphosphonic acid present in brain tissue as well as increases in pro-inflammatory cytokine, Tumor necrosis factor-α (TNF-α), in the brain and peripheral blood plasma. Since TNF-α is elevated in neurodegenerative disorders such as Alzheimer's Disease (AD), in this study, we asked whether glyphosate exposure serves as an accelerant of AD pathogenesis. Additionally, whether glyphosate and aminomethylphosphonic acid remain in the brain after a recovery period has yet to be examined. We hypothesized that glyphosate exposure would induce neuroinflammation in control mice and exacerbate neuroinflammation in AD mice, causing elevated Amyloid-β and tau pathology and worsening spatial cognition despite recovery. We dosed 4.5-month-old 3xTg-AD and non-transgenic (NonTg) control mice with either 0-, 50- or 500-mg/kg of glyphosate daily for 13 weeks followed by a 6-month recovery period. Shockingly, we found that aminomethylphosphonic acid was still detectable in the brains of both 3xTg-AD and NonTg glyphosate exposed mice even after the 6-month recovery period. Glyphosate-dosed 3xTg-AD mice showed reduced survival, increased thigmotaxia in the Morris Water Maze, and significant elevations in Amyloid-β 42, and phosphorylated tau (pTau) at epitopes Threonine 181 and Serine 396. Notably, we found increased pro- and anti-inflammatory cytokines and chemokines persisting in both NonTg and 3xTg-AD brain tissue and in 3xTg-AD peripheral blood plasma in glyphosate exposed mice. Our future work will examine how exposure to glyphosate affects microglia and astrocytes, ultimately resulting in the increased neuroinflammation we observed. Doing so will allows us to further understand the cell autonomous effects of glyphosate exposure in the brain. Taken together, our results show that despite a recovery period, exposure to glyphosate for a short period of time has long-lasting pathological consequences - findings which have implications for those exposed to this herbicide, which is a majority of the US population.

Disclosures: S. Bartholomew: None. **W. Winslow:** None. **R. Sharma:** None. **K. Pathak:** None. **S. Tallino:** None. **J.M. Judd:** None. **H. Leon:** None. **P. Pirrotte:** None. **R. Velazquez:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.02/B108

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

Support: R01AA028924
K08AA024829
R01AG072894
K01AA025713
P50HD103573
R24AA012725

Title: Loss of neuronal lysosomal acid lipase drives amyloid pathology in Alzheimer's disease.

Authors: A. BARNETT[1], J. Y. ZOU[2], S. S. MOY[3], V. D. NIKOLOVA[4], M. E. COLIE[5], R. P. VETRENO[6], ***L. COLEMAN, Jr**[4];
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Abstract: Alzheimer's disease (AD) features the progressive accumulation of pathological amyloid and tau species. However, there is often no clear etiology for the disease, though modifiable behaviors such as smoking, diabetes, and heavy alcohol use increase risk with age. We sought to identify shared underlying cell biological vulnerabilities that promote early AD pathology. To identify convergent molecular abnormalities that drive AD pathogenesis we compared two common midlife risk factors for AD, heavy alcohol use and obesity. Triple transgenic AD mice (3xTg-AD, APP^{Swe}, tau^{P301}, $Psen1^{tm1Mpm}$) received either chronic ethanol (5g/kg/d, 5 days/week, 9-11 months of age) or a western diet (TD.88137, 6 mo-11mo) with assessment at 11 months of age, prior to maximal AD pathology and cognitive deficits. Both chronic heavy alcohol exposure and obesity each increased early intraneuronal $A\beta_{1\text{-}42}$ in frontal cortex, hippocampus, and entorhinal cortex in both sexes. Similar to findings in 3xTg-AD mice, human subjects with alcohol use disorder had increased levels of early AD phosphorylated tau isoforms in the frontal cortex (p-tau214-50% and p-tau181-30%) and the hippocampus (p-tau214-27% and p-tau181-20% increases) along with increased $A\beta_{1\text{-}42}$ in frontal cortex (31%). In AD mice both ethanol and obesity reduced autophagic flux (increased P62, reduced Beclin) and caused lysosomal dysfunction (reduced TFEB, lysosomal acid lipase/LAL, and vATPases). Neuronal LAL loss caused neuronal lysosomal lipid accumulation which opposed Aβ localization to neuronal lysosomes. Neuronal LAL loss preceded Aβ accumulation *in vivo* in WT (amyloid precursor protein in entorhinal cortex) and AD mice (intraneuronal $A\beta_{1\text{-}42}$ in frontal and entorhinal cortices). Inhibition of LAL *in vitro* (LAListat2) and targeted neuronal LAL knockdown *in vivo* (PHP.eB.syn.shLAL) promoted Aβ accumulation and cognitive deficits. Neuronal LAL overexpression *in vivo*, however, (PHP.eB.syn.WPRE.LAL) reduced Aβ pathology and improved cognition. In healthy human brain LAL declined with age across brain regions, with greater reductions in human AD brain and polymerase pausing at the LAL promoter. Together, this identifies the loss of neuronal LAL as an early feature of AD pathogenesis, and implicates LAL as a promising diagnostic, preventative, and/or therapeutic target for AD. (Funded by NIAAA).

Disclosures: A. Barnett: None. **J.Y. Zou:** None. **S.S. Moy:** None. **V.D. Nikolova:** None. **M.E. Colie:** None. **R.P. Vetreno:** None. **L. Coleman:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.03/B109

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

Support: 02 (0425)/21/EMR-II, CSIR-India

Title: Small Molecule Mediator of Synaptic Plasticity & Memory Consolidation Against Aβ42 Oligomeric Toxicity

Authors: *R. ROY[1], S. GHOSH[1], N. MUKHERJEE[2], S. GHOSH[1];
[1]Biosci. & Bioengineering, [2]IDRP-Smart Healthcare, Indian Inst. of Technol. Jodhpur, Jodhpur, India

Abstract: Background: Molecular mechanism behind memory formation wasn't clearly understood until discovery of LTP. LTP mediated consolidation of Long term memory required synaptic GluN2A dependent synthesis of plasticity related proteins (PRP). Aβ42 oligomers downregulate this GluN2A dependent PRP synthesis, causing memory disruption. We report multipotent small molecule NMD8b, which terminate oligomers, revive GluN2A homeostasis, upregulate PRP & restore cognition. **Method:** Library was designed using 3DQSAR model (r^2: 0.98) with 2103 NMDAR specific molecules from ZINC database. Benzofuran core was chosen for reported neuroprotective activity against Aβ42 & affinity for GluN2A. Dotblot, ThT, CD & ITC were done to screen the lead molecule. Immunocytochemical & immunoblot with P0 rat (n=7) hippocampus cells were done to check lead molecule's effect on PRP expression. Electrophysiology of isolated rat pyramidal cells in Mg^{2+} deficient setup was done to detect GluN2A-mEPSP. *In vivo* disease model was improvised by osmotic pump mediated week long intrahippocampal delivery of oligomer. Animals were grouped as Sham, oligomer treated, MK801 treated & lead molecule treated, 11 animals each. Statistical analysis was done using t-test. **Result:** Total 20 molecules were developed. Dotblot showed highest oligomer reduction for NMD8b (78.3% ± 0.05 $p<0.005$). CD, ITC results also checks NMD8b as most effective molecule (82.4% ± 0.05 K_d=28.3nM $p<0.005$). Oligomers cause GluN2A endocytosis, excessive glutamate release & GluN2B mediated depression. Immunocytochemistry showed NMD8b treatment of oligomer effected cells revived GluN2A expression (83.47% ± 0.036 $p<0.001$). NMD8b colocalizes GluN2A & PSD95 rescuing synaptic connection (n=13 $p<0.005$). Oligomers also halts GluN2A mediated intracellular Ca^{2+} release, reducing level of CAMKII, PKC, MAPK & P-CREB. Immunoblot shows NMD8b increases expression of these proteins (n=9 $p<0.005$). NMD8b also fixes GluN2A expression in BRAAK stages (72%± 0.05 n=7 $p<0.001$). Presynaptic glutamate release spontaneously produces mEPSCs in postsynaptic neuron. Oligomers reduces mEPSC amplitude & frequency (13 ± 3 pA & 2.1 ± 0.3 Hz n=11 $p<0.005$). Revival of mEPSCs

(102.2± 12 pA & 8.3 ± 1.3 Hz n=13 $p<0.005$) by NMD8b shows its effect on memory consolidation against oligomers. *In vivo water maze* study showed NMD8b improved escape latency (5.6 ± 0.005s n=11 $p<0.05$) & reduced time (3.4 ± 0.005s n=11 $p<0.05$) required to reach target quadrants compared to oligomer (87.53 ± 0.045s & 66.1 ± 0.05s n=11 $p>0.05$), indicating its efficacy in restoring memory consolidation. **Conclusion:** Result shows NMD8b as a potent lead for Aβ42 mediated memory disruption.

Disclosures: R. Roy: None. **S. Ghosh:** None. **N. Mukherjee:** None. **S. Ghosh:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.04/B110

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

Support: NIH Grant NS100779
Jaya Biosciences, Sponsored Research

Title: Heterozygous loss-of-function mutations in lysosomal enzyme genes are enriched in Alzheimer's disease

Authors: *M. SANDS[1], B. A. BENITEZ[2], C. E. WALLACE[3], M. PATEL[4], C. POTTIER[5], N. GOODWIN[6], K. O'DELL[4], M. NUNEZ[4], C. CRUCHAGA[7], J. R. CIRRITO[8];
[1]Washington Univ. Sch. of Med., Saint Louis, MO; [2]Neurol., Harvard Med. Sch. - BIDMC, Boston, MA; [3]Neurol., Washington Univ. Sch. of Med., Saint Louis, MO; [4]Washington Univ. Sch. of Med., St. Louis, MO; [5]Neurol., Washington Univ. Sch. of Med., St Louis, MO; [6]Jaya Biosci., CLOVIS, CA; [7]Dept. of Psychiatry, Washington Univ. Sch. o, Saint Louis, MO; [8]Neurol., Washington Univ., St. Louis, Saint Louis, MO

Abstract: Homozygous loss-of-function mutations in lysosomal enzyme genes lead to fatal pediatric lysosomal storage diseases. Historically, carriers of lysosomal enzyme gene defects were considered normal. However, the association of heterozygous mutations in the glucocerebrosidase gene (*GBA*) and Parkinson's disease is well established and challenges this dogma. We hypothesized that heterozygous deleterious mutations in lysosomal enzyme genes are associated with adult-onset neurological diseases such as Alzheimer's disease (AD). We performed a human genetic analysis that revealed heterozygous deleterious mutations in at least seven different lysosomal enzyme genes are enriched in AD patients. We validated three of those genes *in vivo*. The first gene was *PPT1,* which encodes the lysosomal enzyme palmitoyl protein thioesterase-1. There was a clear gene-dosage effect when comparing $A\beta_{40}$ levels in brain interstitial fluid (ISF) between WT, heterozygous, and homozygous deficient mice. Eighteen-month-old heterozygous *PPT1* animals exhibited changes in α-, β-, and γ-secretases that favor an amyloidogenic pathway compared to age-matched WT animals. Haploinsufficiency of PPT1 significantly increased the number and distribution of Aβ plaques and the levels of insoluble

$A\beta_{40}$ and $A\beta_{42}$ in the 5xFAD mouse model of AD (5xFAD/PPT1+/-) and decreased the median life span from ~24mo to ~10mo. CNS-directed, AAV-mediated gene therapy initiated in 3.5-month-old 5xFAD/PPT1+/- mice significantly increased life span and improved cognitive function. Heterozygosity of the α-L-iduronidase (*IDUA*) and galactocerebrosidase (*GALC*) genes identified in the genetic analysis directly affected Aβ metabolism *in vivo*. Given that the human genetic analysis may be underpowered for some genes, we hypothesized that the data underestimated the number of lysosomal enzyme genes affecting Aβ processing in AD. Heterozygosity of the N-acetylglucosaminidase (*NAGLU*) and β-glucuronidase (*GUSB*) genes, which were not identified in the genetic analysis, caused changes in ISF $A\beta_{40}$ levels that are similar in direction and magnitude to heterozygous mutations in *PPT1*, *IDUA*, and *GALC*. We are currently determining the effect of heterozygous mutations in additional lysosomal enzyme genes on Aβ metabolism and the efficacy of CNS-directed gene therapy to normalize those defects *in vivo*. These findings are transformative in the fundamental understanding of the role of lysosomal enzyme gene heterozygous mutations in adult-onset neurological diseases and provide a therapeutic option for certain genetically-defined forms of neurodegeneration, including AD.

Disclosures: M. Sands: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jaya Biosciences. **B.A. Benitez:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jaya Biosciences. **C.E. Wallace:** None. **M. Patel:** None. **C. Pottier:** None. **N. Goodwin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jaya Biosciences, Co-Founder. **K. O'Dell:** None. **M. Nunez:** None. **C. Cruchaga:** None. **J.R. Cirrito:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.05/B111

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

Support: NIH R01 AG062500

Title: 3xTg-AD mice exhibit neuropathological sex discrepancies that correlate with circulating choline levels

Authors: *J. M. JUDD[1], F. MISTRY[2], W. WINSLOW[2], S. TALLINO[2], J. TURK[2], R. VELAZQUEZ, Jr.[2];
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease that is characterized by a progressive loss of memory and other cognitive abilities. Neuropathologically, AD is

characterized by amyloid-beta (Aβ) plaques, neurofibrillary tau tangles, and neuroinflammation. The prevalence of AD is increasing, thus understanding both risk and protective factors could help mitigate the rise of this disease. Our lab has identified that a deficiency of dietary choline, a b-like vitamin nutrient, can increase AD risk, while higher intake and circulating levels are protective. The 3xTg-AD mouse model of AD, which carries three human AD mutations, APP Swedish, MAPT P301L, and PSEN1 M146V, resulting in Aβ pathology starting at 6 months and widespread Aβ and tau pathology by 12 months of age, is commonly used in preclinical AD studies. Notably, most published work uses only female 3xTg-AD mice given the inconsistent neuropathology observed in males. Here, we sought to better understand how endogenous circulating blood choline levels may be associated with the sex discrepancies observed in AD pathology in 3xTg-AD mice. Body weight, food consumption, and blood plasma samples were collected at 1, 3, 6, 9, and 12 months of age. A behavioral battery was performed to assess anxiety-like behavior, using the elevated plus maze, motor learning, using the rotarod, and hippocampal and cortical dependent cognition, using the IntelliCage, at 13.48 ± 0.12 months of age. Following behavior, hippocampal and cortical tissue were collected to assess neuropathology. NonTg males exhibited higher food consumption, which was reflected in their higher body weight compared to all other groups. Across the lifespan, 3xTg-AD mice showed lower circulating blood choline levels than NonTg mice, and male mice exhibited higher circulating blood choline levels than females. 3xTg-AD females had higher levels of both Aβ and tau pathology than their male counterparts and higher pathology correlated with lower blood choline levels. 3xTg-AD showed higher anxiety-like behavior, but better performance on the second day of rotarod than NonTg. Across IntelliCage tasks, NonTg males showed the most engagement, with higher corner visits and licks for water than other groups. In the place preference task, females showed lower percentage of correct responses than males. Consistent with our recent finding that low circulating blood choline levels are associated with increased neuropathology in human AD, these findings illustrate that the lower circulating blood choline levels through the lifespan in female 3xTg-AD mice may be associated with the sex discrepancies in neuropathology observed in this mouse model.

Disclosures: J.M. Judd: None. **F. Mistry:** None. **W. Winslow:** None. **S. Tallino:** None. **J. Turk:** None. **R. Velazquez:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer’s Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.06/B112

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

Support: NIH R01AG059627

Title: Adulthood dietary choline supplementation modestly lowers metabolic symptoms related to Alzheimer’s disease risk in the Ts65Dn model of Down syndrome

Authors: *S. TALLINO, R. ETEBARI, H. LEON, I. SEPULVEDA, S. BARTHOLOMEW, R. VELAZQUEZ, Jr.;
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Abstract: Down syndrome (DS) occurs in 1/700 live births and is the most common cause of early onset Alzheimer's disease (AD). Dietary choline intake has been proposed as a modifiable factor for AD and DS; choline is synthesized in the liver, but endogenous synthesis is not enough for the body's needs, with recommended intake set in 1998 to prevent hepatic steatosis. We have shown that AD mouse models with inadequate dietary choline have exacerbated AD pathology, and low circulating choline in humans correlates with high pathological AD burden. Perinatal choline supplementation (Ch+) studies have been performed in the Ts65Dn model of DS (Jackson Strain #005252), which protected offspring against AD-relevant pathologies such as loss of cholinergic basal forebrain (BF) neurons and decline in hippocampal-dependent cognition. To date, two studies showed that adulthood dietary Ch+ in AD models ameliorates AD pathology and improves cognition; however, Ch+ in adult Ts65Dn mice has not been explored. Previously we found that adulthood Ch+ failed to reverse hippocampal-dependent cognitive outcomes in Ts65Dn mice, and did not affect age-dependent decline in circulating choline levels, though it modestly improved fasting glucose and lowered age-related weight gain. Trisomic Ts65Dn mice and disomic littermate controls (n = 16-18 per diet per genotype, balanced by sex) were fed choline normal (ChN; 1.1 mg/kg) or Ch+ (5 mg/kg) diets starting at 4.5 months (mo), with behavioral testing at 13 mo and tissue collection at 14 mo. Here, we show that in a subset of trisomic females (n = 6-8 per diet), Ch+ modestly increased performance in a reverse place preference task via the automated IntelliCage behavioral phenotyping system, with no effect of Ch+ on other cognitive tasks such as attention, impulsivity, or conditioned avoidance. In additional subsets of animals (n=6-8 per sex, diet, and genotype) we further show that, while steatosis correlated with weight gain, Ch+ did not lower hepatic steatosis, and Ch+ did not alter A1C levels despite lowering fasting glucose. We also found no difference between genotypes or diets in the colocalization of microglial activation markers in the hippocampus, and unbiased stereological analysis of BF cholinergic neurons (medial septum and vertical limb of the diagonal band) were unchanged by Ch+. In conclusion, we reiterate that perinatal and/or early-life Ch+ is crucial in DS, as Ch+ in adulthood provides only minor metabolic benefits and fails to rescue neuropathological measures in the Ts65Dn mouse. Whether the DS population meets dietary choline needs has yet to be examined, highlighting the need for further investigation.

Disclosures: S. Tallino: None. **R. Etebari:** None. **H. Leon:** None. **I. Sepulveda:** None. **S. Bartholomew:** None. **R. Velazquez:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.07/B113

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

Support: R42NS129400

Title: Validating the efficacy of a novel potent Dyrk1a inhibitor (DYR533) in the Ts65Dn mouse model of Down Syndrome

Authors: *J. TURK[1], W. WINSLOW[1], S. TALLINO[1,2], J. M. JUDD[1], S. BARTHOLOMEW[1,2], F. MISTRY[1], C. HULME[3,4], T. DUNCKLEY[1,5,2], R. VELAZQUEZ, Jr.[1,5,2];
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Abstract: The majority of individuals with Down Syndrome (DS) develop Alzheimer's Disease (AD) pathology including amyloid beta (Aβ) plaques and neurofibrillary tangles by the fifth decade of life. Several proteins implicated in AD pathology have triplicated genes in DS, including dual-specificity tyrosine phosphorylation-regulated kinase-1a (Dyrk1a). Dyrk1a phosphorylates both the amyloid precursor and tau protein and has been shown to be upregulated in postmortem brain tissue of patients with AD rendering this protein an attractive therapeutic target to reduce pathogenesis. Our previous work has shown that a novel Dyrk1a inhibitor, termed DYR533, reduces Aβ and tau pathogenesis in the 3xTg-AD and PS19 mouse models. Here, we evaluated the efficacy of DYR533 in the Ts65Dn mouse model of DS. Starting at 4.5 months of age, disomic (2N) and trisomic (3N) Ts65Dn mice received daily intraperitoneal injections of either 0.625-, 2.5- or 10- mg/kg DYR533 or a vehicle control for approximately 3.5 months. Silmitasertib, a commercially available Dyrk1a inhibitor, was also included at a dosage of 25mg/kg to serve as a comparison and benchmark for efficacy. Mice underwent a battery of behavioral testing including elevated plus maze, rotarod and radial arm water maze. At 8 months, mice were euthanized and the basal forebrain and hippocampus, key brain regions affected in DS and the Ts65Dn mouse, were harvested for neuropathological assessment. Basal forebrain and hippocampal protein homogenates were probed using Enzyme-linked immunoassays for Aβ40 and 42, Dyrk1a levels, and phosphorylated Tau (pTau) at threonine (Thr 181). In both the 2N and 3N mice, treatment with DYR533 reduced soluble fractions of basal forebrain and hippocampal Dyrk1a, Aβ40 and Aβ42 as well as pTau Thr181. Notably, beneficial effects were significantly higher in the DYR533 dosed mice compared to the Silmitasertib treated mice. Collectively, we demonstrate that the optimized small molecule Dyrk1a inhibitor, DYR533, reduces Dyrk1a, Aβ and pTau in the DS Ts65Dn mouse model. This work sets the stage for future development and testing of DYR533 as a potential therapeutic for individuals with DS and AD.

Disclosures: J. Turk: None. **W. Winslow:** None. **S. Tallino:** None. **J.M. Judd:** None. **S. Bartholomew:** None. **F. Mistry:** None. **C. Hulme:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iluminos Therapeutics. **T. Dunckley:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iluminos Therapeutics. **R. Velazquez:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.08/B114

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

Title: The glycation-lowering formulation Gly-Low improves Alzheimer's disease phenotypes in APOE4 EFAD mice

Authors: C. MCGILL[1], K. KANESHIRO[2], A. CHRISTENSEN[1], P. KAPAHI[2], ***C. PIKE**[1]; [1]USC, Los Angeles, CA; [2]Buck Inst. for Res. on Aging, Novato, CA

Abstract: Age and apolipoprotein E ε4 allele (*APOE4*) genotype are primary risk factors for late-onset Alzheimer's disease (AD). These risk factors are also associated with elevated levels of advanced glycation end products (AGEs), which are proteins or lipids that contain an added sugar that results in irreparable damage to the molecules, compromising their structural and functional integrity. Deleterious effects of AGEs may contribute to the development of AD and related disorders, in which case inhibition of AGEs would represent a potential therapeutic strategy. Previous work showed that treatment of mice with a specific formulation of nicotinamide, lipoic acid, thiamine, pyridoxamine, and piperine (called Gly-Low) lowered glycation and the formation of AGEs in mice, along with an extension of lifespan, reduced food intake, and improved insulin sensitivity. Since Gly-Low acts upon systemic pathways that have also been associated with AD, we considered that Gly-Low may constitute a potential intervention strategy. Further, because *APOE* status affects glycation propensities, Gly-Low protection may be modulated by *APOE* genotype. To examine the ability of Gly-Low to attenuate the development of AD-related phenotypes, we treated 2.5-month-old AD transgenic mice homozygous for knock-in of either human *APOE3* or *APOE4* (E3FAD and E4FAD, respectively) for 16 weeks with vehicle or Gly-Low. Our results indicate *APOE* genotype differences in the impact of Gly-Low on a range of systemic and neural outcomes. Both E3FAD and E4FAD mice exhibited reduced food intake and body weight, with E3FAD mice showing greater improvements in glucose tolerance and body fat reduction. Interestingly, Gly-Low treatment yielded neural improvements in an *APOE*-dependent manner, with greater reductions in β-amyloid and higher behavioral performance in the novel object recognition task in E4FAD compared to E3FAD mice. These data demonstrate that *APOE* genotype influences the impact of the beneficial effects of Gly-Low. The well-known importance of age and the progeroid effect of *APOE4* on AD highlight the potential to use geroscience approaches in the prevention and treatment of AD.

Disclosures: C. McGill: None. **K. Kaneshiro:** None. **A. Christensen:** None. **P. Kapahi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Juvify. **C. Pike:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.09/B115

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

Support: NIA R01 AG084485

Title: Metabolic and AD markers are improved by longevity-enhancing treatments in aged male EFAD mice

Authors: *A. CHRISTENSEN[1], C. MCGILL[2], A. ZAIDI[1], C. J. PIKE[3];
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Abstract: The greatest risk factor for Alzheimer's disease (AD) is aging. The e4 allele of apolipoprotein E (*APOE4*) is the primary genetic risk factor for AD. *APOE* genotype regulates aging and longevity too. *APOE4* has been associated with decreased longevity in both humans and rodents. Many of the pathways disrupted during aging and by *APOE4* genotype are implicated in AD pathogenesis, suggesting that therapeutics known to improve health- and lifespan may be repurposed to function as effective interventions for AD, especially in the context of *APOE4*. To investigate this topic, we studied the independent and combined efficacies of two longevity treatments in EFAD mice, a rodent with knock-in of human *APOE3* or *APOE4* crossed to the 5xFAD mouse model of AD. The first intervention was Fasting Mimicking Diet (FMD), a version of caloric restriction that reduces caloric intake for 4 consecutive days starting every 2 weeks while maintaining the intake of micronutrients. The second intervention was 17α-estradiol (17αE2), a naturally occurring low potency estrogen and stereoisomer of the primary estrogen, 17β-estradiol. 17αE2 has been shown to increase lifespan as well as beneficially regulate inflammatory and metabolic pathways in male mice. Sixteen-month-old male *APOE3* and *APOE4* EFAD mice were randomized into one of four treatment groups: (1) vehicle + *ad libitum* diet; (2) vehicle + FMD; (3) 17αE2 + *ad libitum* diet; or (4) 17αE2 + FMD. After nine weeks of treatment, a range of systemic and neural outcomes were tested. Untargeted plasma metabolomics identify changes in several important metabolic markers by FMD and 17αE2. Further, unbiased RNA sequencing of the hippocampus has revealed several pathways of interest. Together with the changes in AD neuropathology, this data has important implications and suggests that continued investigation of longevity drugs for the treatment of AD may be warranted.

Disclosures: A. Christensen: None. **C. McGill:** None. **A. Zaidi:** None. **C.J. Pike:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.10/B116

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

Support: NIA AD/ADRD F31 AG084279

Title: Protection against APOE4-associated aging phenotypes with the longevity-promoting intervention 17a-estradiol: impact of sex

Authors: *C. MCGILL[1], A. CHRISTENSEN[2], S. NAMVARI[2], C. E. FINCH[2], B. BENAYOUN[2], C. J. PIKE[3];
[1]USC, University of Southern California, CA; [2]USC, Los Angeles, CA; [3]USC Leonard Davis Sch. of Gerontology, USC, Los Angeles, CA

Abstract: Age, apolipoprotein E (*APOE*) genotype, and biological sex are three significant, unmodifiable risk factors for late onset Alzheimer's disease (AD). In the US, approximately two-thirds of persons with AD carry an *APOE4* allele, and two-thirds of persons with AD are women. The risk of AD in women with two copies of *APOE4* is increased up to a 15-fold compared to *APOE3* homozygous women. While age, *APOE* genotype, and biological sex are unmodifiable, their phenotypes implicated in promoting AD risk may be targets for intervention. Both age and *APOE4* genotype are associated with decreased metabolic function and altered inflammatory tone, which in turn can increase AD vulnerability. The NIA Interventions Testing Program found that treatment with the weak estrogen 17α-estradiol (17αE2) increased healthspan and lifespan in mice, although these effects were limited to male mice. Our recent work showed genotype-dependent effects of 17αE2, with 17αE2 generally providing greater healthspan benefits to *APOE4* males. The lack of lifespan extension in female mice does not necessarily indicate the absence of beneficial healthspan effects. Here, we investigated the possibility that the *APOE*-dependent, AD-relevant healthspan benefits induced by 17αE2 in male mice may also extend to females. Specifically, we treated 12-month-old *APOE3* and *APOE4* targeted replacement female mice for 6 months with chow containing 0 vs. 14.4ppm 17αE2. Our initial results indicate metabolic benefits in 17αE2-treated *APOE4* mice including decreases in body weight and hepatic steatosis and increased lean mass suggesting a positive *APOE4* bias in 17αE2 protective effects in female mice. Ongoing analyses include assessment of systemic and neural effects of 17αE2, including metabolic cages, cytokine measurement, behavioral effects, and neuroinflammation. These findings address the impact of chromosomal sex on established protective effects of a longevity-promoting intervention against APOE4 phenotypes, which have significant relevance to the prevention of AD and related disorders.

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Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.11/B117

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

Support: AS-KPQ-111-KNT

Title: A potential role of NPAS4 in mouse models of Alzheimer's disease

Authors: *C.-Y. LIN[1,2], C.-P. CHANG[1,2], Y. CHERN[1,2];
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Abstract: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder in aging populations, characterized by mitochondrial dysfunction, oxidative stress, β-amyloid plaques, neurofibrillary tangles, neuroinflammation, and synaptic loss that cause cognitive decline and memory impairment. ENT1 is a bidirectional adenosine transporter and has been implicated in AD pathology. We have previously demonstrated that blockage of ENT1 using an orally active adenosine analogue (J4) is effective in markedly ameliorating the impairment of cognitive functions in two distinct mouse models (APP/PS1 and Thy-Tau22) of AD. In the present study, we further demonstrated that treatment with J4 in these two AD mice at the symptomatic stage improved mitochondrial function, reduced oxidative stress, and mitigated Aβ and tau pathology. We also assessed the disease state of these two AD mice by positron emission tomography (PET) imaging using [^{18}F]-florbetaben, [^{18}F]-THK5351, or [^{18}F]-BCPP-EF, which detects the level of β-amyloid plaques, tau protein aggregates, and mitochondrial mass, respectively. Our results confirmed the therapeutic effect of J4 and the effectiveness of PET to monitor AD progression non-invasively. RNAseq analysis of the hippocampus of symptomatic APP/PS1 and Thy-Tau22 mice revealed that downregulation of the Neuronal PAS Domain Protein 4 (NPAS4) is a common feature shared by these two different AD mice. NPAS4 is a transcription factor crucial for synaptic activity and cognitive function. Treatment with J4 in both symptomatic AD mice not only restored the impaired cognitive function but also enhanced the NPAS4 level in the diseased hippocampus. These findings support that J4 is an effective therapeutic drug for AD and that NPAS4 is a novel drug target for AD.

Disclosures: C. Lin: None. **C. Chang:** None. **Y. Chern:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.12/B118

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

Support: AS-KPQ-111-KNT

Title: Application of a novel equilibrative nucleoside transporter 1 (ENT1) inhibitor J4 on cognitive deficits and sleep disruptions in sporadic Alzheimer's mice

Authors: *F.-C. CHANG[1], M. LEE[2], Y.-C. HUANG[1], P.-L. YI[3], T.-Y. LEE[4], C.-Y. LIN[5], Y. CHERN[6];
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Abstract: Alzheimer's disease (AD), a prevalent neurodegenerative condition in the elderly lacking effective treatment, is characterized by the accumulation of amyloid-beta plaques and neurofibrillary tangles, leading to cognitive decline and memory impairment. Sleep disturbances are not only prevalent in AD patients but also exacerbate the disease progression, forming a bidirectional relationship with AD pathology. Our study aimed to establish a reliable sporadic AD (sAD) animal model using intracerebroventricular (icv) injection of streptozotocin (STZ) to induce insulin resistance and intrahippocampal (ih) injection of amyloid-beta (Aβ1-42) to mimic AD pathology, and to assess the therapeutic potential of a novel equilibrative nucleoside transporter (ENT)1 inhibitor J4 on sAD and its associated sleep disruptions. We evaluated pathological markers including amyloid-beta plaques, phosphorylated tau proteins, and indicators of apoptosis and DNA damage, cognitive function using Morris water maze (MWM) and novel object recognition (NOR) tasks, and sleep-wake activities and architectures via electroencephalogram (EEG) and electromyogram (EMG) recordings following J4 administration. Additionally, we investigated its effects on physiological sleep-wake activity and insomnia in mice, employing adenosine receptor antagonists (A1R antagonist DPCPX or A2AR antagonist SCH 58261) and examining c-fos expression in GABAergic neurons of the ventrolateral preoptic area (VLPO). Administration of caffeine and stress (change of cage bedding) were used to induce acute insomnia. Our findings demonstrated that J4 mitigated oxidative stress, DNA damage, cholinergic neuronal loss, and cognitive deficits in sAD mice, while also improving sAD-induced sleep disturbances. Specifically, J4 enhanced non-rapid eye movement (NREM) sleep, mediated by adenosine receptors and GABAergic neurons in VLPO in naïve mice. Moreover, J4 effectively alleviated caffeine- and stress-induced insomnia. Following a head-to-head comparison with Lemborexant, our findings revealed that J4 demonstrated superior hypnotic efficacy without altering slow wave activity during NREM sleep. In conclusion, our results suggest that J4 holds promise as a therapeutic agent for sAD and its associated sleep disruptions, potentially through modulating adenosine receptors and GABAergic neurons within the VLPO, offering a multifaceted approach to tackling the complex pathology of AD.

Disclosures: F. Chang: None. **M. Lee:** None. **Y. Huang:** None. **P. Yi:** None. **T. Lee:** None. **C. Lin:** None. **Y. Chern:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.13/B119

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

Support: NIA Grant 5K00AG068428-04
Bluefield project to cure FTD

Title: Block of Sortilin Binding in Progranulin Gene Therapy Increases Progranulin Levels and Corrects Lipid Abnormalities, Behavioral Phenotypes, and Neurodegeneration Biomarkers in Progranulin-Deficient Mice

Authors: *S. FOX[1], S. KASHYAP[2], A. TADEPALLI[3], M.-M. B. COOPER[4], R. V. FARESE[5], A. E. ARRANT[6], E. D. ROBERSON[7];
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Abstract: Progranulin is a secreted protein that is transported to the lysosome through receptors including sortilin. Within the lysosome, progranulin serves as a chaperone for lysosomal enzymes to facilitate the degradation of proteins and lipids. Homozygous loss-of-function mutations in progranulin lead to neuronal ceroid lipofuscinosis (NCL), while heterozygous loss-of-function mutations cause frontotemporal dementia (FTD). The loss of progranulin protein leading to neurodegeneration points to a potential therapy where progranulin protein can be restored using AAV-gene therapeutics. Previous studies have demonstrated the effectiveness of AAV-progranulin tagged at the carboxy-terminus, disrupting its interaction with sortilin. This led us to hypothesize that transduction of progranulin lacking its carboxy-terminal sortilin-binding domain might be a more effective alternative to progranulin with intact sortilin binding. We compared treating progranulin knockout mice with carboxy-terminally blocked progranulin, progranulin with intact sortilin binding, or GFP control. We used multiple outcome measures including immunohistochemistry, microdialysis, lipidomics, machine learning behavioral assays, and biomarker analysis to assess the impact of carboxy-terminal blockade. Progranulin with a blocked carboxy-terminal increased progranulin levels at the injection site through immunohistochemistry and microdialysis. Additionally, both progranulin with and without its sortilin binding corrected BMP deficiency and ganglioside accumulation, with the carboxy-terminal blocked progranulin more effective in cerebellar BMP deficiency and cortical and thalamic ganglioside accumulation. Interestingly, only the carboxy-terminal blocked progranulin reduced plasma NfL, a neurodegeneration biomarker, in progranulin knockout mice. Machine learning behavioral analysis revealed that mice treated with carboxy-terminally blocked progranulin resembled wild-type mice, while those with intact sortilin binding resembled progranulin knockout mice. These findings indicate that blocking the carboxy-terminus of progranulin enhances the effectiveness of progranulin gene therapy.

Disclosures: S. Fox: A. Employment/Salary (full or part-time):; University of Alabama at Birmingham. 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.; NIA F99/K00. **S. Kashyap:** None. **A. Tadepalli:** None. **M.B. Cooper:** None. **R.V. Farese:** None. **A.E. Arrant:** None. **E.D. Roberson:** A. Employment/Salary (full or part-time):; University of Alabama at Birmingham. 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.; Grants from NIH, Bluefield Project to Cure FTD, Alzheimer's Drug Discovery Foundation, site PI for clinical trials with Eisai and Lilly. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Owner of IP related to tau, royalties on mouse model licensed to Genentech. F. Consulting Fees (e.g., advisory boards); Member of SAB for AGTC, Member of DMC for Lilly, Member of Editorial Board for SfN.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.14/B120

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

Title: Block of sortilin binding in progranulin gene therapy enhances rescue of microgliosis and microglial lipofuscinosis in progranulin-deficient mice

Authors: *A. TADEPALLI[1], S. N. FOX[2], S. KASHYAP[2], C. F. MURCHISON[2], A. E. ARRANT[3], E. D. ROBERSON[4];
[1]UAB Neurosciences Programs, Birmingham, AL; [2]Univ. of Alabama at Birmingham, Birmingham, AL; [3]Neurol., Univ. of Alabama At Birmingham, Birmingham, AL; [4]Neurol., Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: Loss-of-function mutations in the progranulin (*GRN*) gene which encodes a lysosomal glycoprotein, lead to neurodegeneration. Individuals with mutations in both progranulin alleles have a complete loss of the progranulin protein resulting in a lysosomal storage disorder, neuronal ceroid lipofuscinosis (NCL). Progranulin haploinsufficiency notably causes frontotemporal dementia (FTD), an early-onset dementia characterized by degeneration of the frontal and temporal lobes of the brain. Both patient populations exhibit gliosis, increased levels of lysosomal proteins, and lipofuscinosis. Progranulin-deficient mice exhibit similar pathologies with increased gliosis and lipofuscinosis throughout the brain. Restoration of the progranulin protein is a rational therapeutic strategy using AAV-progranulin gene therapy. Previous data has shown that AAV-progranulin gene therapy with a blocked carboxy terminus to block progranulin's interaction with sortilin corrects lipofuscinosis and microgliosis in progranulin-deficient mice. This led us to ask whether blocking progranulin's carboxy-terminal domain would be a more effective therapeutic than progranulin with normal sortilin binding in correcting these phenotypes. To answer this question, we compared the effects of AAVs expressing progranulin with and without carboxy-terminal modifications that block sortilin binding. We

found superior correction in several outcome measures with the carboxy terminally blocked progranulin, including more effective correction of microgliosis, microglial lipofuscinosis, and microglial morphology. These findings suggest that blocking progranulin's carboxy terminus and its interaction with sortilin enhances progranulin gene therapy's ability to correct microgliosis and microglial lipofuscinosis.

Disclosures: A. Tadepalli: None. **S.N. Fox:** None. **S. Kashyap:** None. **C.F. Murchison:** None. **A.E. Arrant:** None. **E.D. Roberson:** A. Employment/Salary (full or part-time):; UAB. 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.; Grants from NIH, Bluefield Project to Cure FTD, Alzheimer's Drug Discovery Foundation, site PI for clinical trials with Eisai and Lilly. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Owner of IP related to tau, royalties on mouse model licensed to Genentech. F. Consulting Fees (e.g., advisory boards); Member of SAB for AGTC, Member of DMC for Lilly, Member of Editorial Board for SfN.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.15/B121

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

Support: Reynolds Fund, Oregon State University Foundation

Title: Heterozygous 5xFAD mice have increased fragmented sleep at a very early age

Authors: *K. J. KIM[1], A.-R. L. VILLEGAS[2], H. KLOEFKORN[3], K. R. MAGNUSSON[4]; [2]Chemical, Biological, and Enviromental Engin., [3]Chemical, Biological, and Envrn. Engin., [4]Dept Biomed Sci, Coll Vet Med. & Linus Pauling Inst., [1]Oregon State Univ., Corvallis, OR

Abstract: Alzheimer's disease (AD) is an incurable brain disease that is the most common form of dementia. There is a critical need to design treatments that can intervene in early events to prevent or delay the onset of the disease. Our recent findings showed that the 5xFAD mouse model, which was believed to develop synaptic dysfunction only at 6 months of age, actually showed increased N-methyl-D-aspartate receptor (NMDARs) subunit responses by 0.5-1 months of age, but decreased responses by 2 months. The 5xFAD mouse model has five mutations, linked to familial (inherited) AD, which leads to amyloid overexpression. Based on early mitochondrial and electrophysiology changes, we hypothesized that 5xFAD heterozygotes (HET) would show non-invasive behavioral alterations early in development. Sleep in males and females at 1 and 2 months (n=3-6) was measured via previously validated non-invasive sensors [Kloefkorn 2020, Kloefkorn 2022] for 12 hours (6pm-6am) to score 3-stage sleep/wake: wake, non-rapid eye movement sleep (NREM), and REM sleep. During sleep recordings, mice were

pair-housed by sex in home cages with a temporary insert enabling sight, smell, and sound interactions. Sleep was scored manually in 10-second epochs in Spike2 (Cambridge Electronic Design, Inc.). A custom MATLAB script calculated these sleep measures: percentage times spent asleep or in REM sleep, sleep fragmentation index (SFI), microarousal index, REM and NREM sleep bout durations, and REM sleep onset latency. T-tests and ANOVAs were performed between genotypes or genotypes and age. HET animals at 1 month had a higher SFI than wild type (WT) at 1 month (p=.030) and HET at 2 months (p=.043). Male HET mice had longer sleep events (p=.006) at 2 months relative to their 1 month time point, indicating a resolution of fragmented sleep. Both female and male HET mice spent less % time in REM sleep (p=.042 and p=.003, respectively) at 2 months relative to their 1 month time point, but WT animals did not change. Female HET mice had fewer sleep events with REM sleep (p=.037) at 2 months than at 1 month. Together, these suggest REM sleep may be sensitive to continued change along the AD pathogenesis. Female WT mice had longer sleep events (p=.021) at 2 months relative to their 1 month time point. At an early age, there appeared to be important differences in sleep behavior in the 5xFAD heterozygous mice, including differences between 1 and 2 months of age, which may mirror other early changes seen in 5xFAD mice. These non-invasive behavioral measures could be useful for monitoring treatment effects on early disease progression longitudinally in AD mouse models. This work was funded by the Reynolds Fund, OSU Foundation.

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Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.16/B122

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

Support: State Research Programme (project "BioMedPharm" nr. VPP-EM-BIOMEDICĪNA-2022/1-0001).

Title: Investigating behavioral outcomes following active immunization of mice with chimeric AP205 VLPs targeting pyrAβ toxic species

Authors: *V. PILIPENKO[1], J. UPITE[1], I. LIEKNINA[3], D. SKRASTINA[3], L.-M. MORCHE[2], B. JANSONE[1], K. TARS[3];
[1]Dept. of Pharmacol., [2]Fac. of Med. and Life Sciences, Univ. of Latvia, Riga, Latvia; [3]Latvian Biomed. Res. Ctr., Riga, Latvia

Abstract: Background. Active immunization therapy could combat Alzheimer's disease by triggering the host to produce antibodies over time, avoiding the requirement for regular administration and being more economically feasible and less invasive than passive

immunization. A promising biotechnological approach for vaccination involves utilizing virus-like particles (VLPs) - hollow, non-infectious protein structures derived from viruses, acting as carriers for the target antigen. RNA bacteriophage-based VLPs possess robustness and simplicity of production and are extensively explored in vaccine development. **Methods.** In this study, we used active immunotherapy with chimeric VLPs derived from the bacteriophage AP205. Dense presentation of Aβ(3-8) epitopes on AP205 VLPs (VLP-pyrAb) surface enhances B-cell activation via receptor cross-linking. Co-expression with soluble glutaminyl cyclase ensures in vivo pyroglutamate modification of the Aβ epitope N-terminus, mimicking the natural toxic Aβ species. 5xFAD mice (n=13/group) received four injections of adjuvant tha was mixed with either VLP-pyrAb, VLP, or phosphate-buffered saline at regular intervals starting at 2 months of age. Blood titers for pyrAβ(3-8) and AP205 VLP were determined using an enzyme-linked immunosorbent assay biweekly for the first 45 days and then biweekly during the study. The efficacy of the vaccine was then determined in a battery of behavioral tests at two time points: 6 and 8 months of age. Open field (OF), spontaneous alternation (SA), Morris water maze (MWM), and elevated o-maze (EOM) tests were employed. MWM was performed for 5 days, including 4 consecutive days of training (platform submerged 1 cm under water) and a probe trial on day 5 with the platform taken out. One-way analysis of variance followed by Holm-Sidak's post-hoc test was performed to determine significant changes between studied groups. **Results.** In the OF test, the total distance traveled and time spent in the center zone did not significantly change between groups. In the EOM test, the number of entries into closed and open arms, and time spent in both arms did not differ between all tested groups. The alteration index was similar in all groups at both time points in the SA test. Spatial learning (i.e., escape latency) decreased in all groups during MWM training but was not significantly altered between groups. Moreover, spatial learning - time spent in the platform zone and the number of platform zone crossings - was also similar in all studied groups. **Conclusions.** Pyroglutaminilated Aβ(3-8)-VLP-based vaccine administration did not alter the early behavioural response in 5xFAD mice.

Disclosures: V. Pilipenko: 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.; State Research Programme (project "BioMedPharm" nr. VPP-EM-BIOMEDICĪNA-2022/1-0001).. **J. Upite:** None. **I. Lieknina:** 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.; State Research Programme (project "BioMedPharm" nr. VPP-EM-BIOMEDICĪNA-2022/1-0001).. **D. Skrastina:** None. **L. Morche:** None. **B. Jansone:** 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.; State Research Programme (project "BioMedPharm" nr. VPP-EM-BIOMEDICĪNA-2022/1-0001). **K. Tars:** 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.; State Research Programme (project "BioMedPharm" nr. VPP-EM-BIOMEDICĪNA-2022/1-0001)..

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.17/B123

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

Support: This work is supported by a grant from the National Institutes for Aging (1RF1AG074256-01A1 to A.K.S.)

Title: Intermittent Administrations of EVs from hiPSC-NSCs Restrain Neuroinflammation and Maintain Better Cognitive and Mood Function for Extended Periods in 5xFAD Mice

Authors: *L. MADHU, Y. SOMAYAJI, S. RAO, V. RAO, M. KODALI, J. ELIZABETH JAMES, Z. SYED, B. SHUAI, G. SHANKAR, M. KIRMANI, X. RAO, A. K. SHETTY; Inst. for Regenerative Medicine, Dept. of Cell Biol. and Genetics, Texas A&M Univ. Sch. of Medicine, Col. Station, Texas, USA., College Station, TX

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that leads to severe cognitive and memory decline. Neuroinflammation plays a vital role in the development and progression of AD. Extracellular vehicles (EVs) released by neural stem cells (NSCs) have emerged as a promising therapeutic approach for reducing neuroinflammation. This study examined the efficacy of intermittent intranasal (IN) administrations of extracellular vehicles (EVs), purified through chromatographic methods from cultures of human induced pluripotent stem cell (hiPSC)-derived neural stem cells (NSCs), for reducing neuroinflammation and maintaining better cognitive function for extended periods in 5XFAD mice, a model of early-onset and familial AD. Three-month-old 5xFAD mice received IN administrations of hiPSC-NSC-EVs (~30 billion EVs) or the vehicle (once monthly for 5 months). A month after the final dose of EVs (i.e., at 8 months of age), the cognitive and mood functions were measured through a series of neurobehavioral tests, and animals were euthanized for quantification of markers of oxidative stress, neuroinflammation, and amyloid plaque deposition. AD mice receiving intermittent hiPSC-NSC-EVs displayed improved abilities to discern minor changes in the environment in an object location test, pattern separation in a pattern separation test, and spatial recognition memory in an object-in-place test, compared to AD mice receiving intermittent vehicle treatment. Besides, hiPSC-NSC-EVs-treated AD mice displayed no anhedonia in a sucrose preference test compared to significant anhedonia in AD mice receiving vehicle treatment. Brain tissue analyses revealed that AD mice receiving intermittent hiPSC-NSC-EVs exhibited reduced microglial clusters, astrocyte hypertrophy, percentage of microglia presenting CD68 and NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome complexes and extent of amyloid-beta plaques in the hippocampus, compared to vehicle-treated AD mice. Moreover, compared to vehicle-treated AD mice, the brain tissues from hiPSC-NSC-EVs-treated AD mice displayed significant reductions in concentrations of oxidative stress markers (malondialdehyde and protein carbonyls), and proinflammatory cytokines (tumor necrosis factor-alpha and interleukin-1 beta). The results underscore that intermittent intranasal administration of hiPSC-NSC-EVs is an efficient approach to maintaining better cognitive and

mood function for extended periods in AD, as such treatment effectively restrains the progression of oxidative stress and neuroinflammation in AD.

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Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.18/B124

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

Support: This work is supported by a grant from the National Institutes for Aging (1RF1AG074256-01A1 to A.K.S.)

Title: In administration of EVs from hiPSC-NSCs in 5xFAD mice modulates mTOR signaling, autophagy, and BDNF-CREB signaling.

Authors: *S. KOTIAN, L. N. MADHU, R. UPADHYA, S. RAO, S. ATTALURI, Y. SOMAYAJI, B. SHUAI, A. K. SHETTY;
Inst. for Regenerative Med., Dept. of Cell Biol. and Genet., Texas A&M Univ. Sch. of Med., Col. Station, Texas, USA., College Station, TX

Abstract: Alzheimer's disease (AD), a type of dementia typified by the accumulation of amyloid plaques and the formation of neurofibrillary tangles, leads to neurodegeneration and severe cognitive decline. Early pathophysiological changes in AD include hyperactivation of the mechanistic target of rapamycin (mTOR) signaling, increased oxidative stress, impaired autophagy, and hippocampal neurogenesis decline. Hippocampal neurogenesis is essential for forming new memories and pattern separation, but it significantly declines in AD. This study investigated the effectiveness of extracellular vesicles (EVs) released by human-induced pluripotent stem cell (hiPSC)-derived neural stem cells (hNSCs) for modulating mTOR signaling, oxidative stress, autophagy, and neurogenesis in 5x familial AD (5xFAD) mice, a model of early-onset AD. Three-month-old 5xFAD mice received intranasal administrations of either hiPSC-NSC-EVs (~30 billion/week for two weeks, AD-EVs group) or the vehicle (AD-Veh group). At 3.5 months, 5'-bromodeoxyuridine (BrdU) was administered for seven days to measure the extent of neurogenesis. Three months later, brain tissue sections were processed for visualizing the markers of neurogenesis (BrdU, BrdU-NeuN, and doublecortin), mTOR signaling (pS6), and autophagy (p62). In addition, hippocampal tissue lysates were processed to measure vital proteins associated with mTOR signaling (pan-mTOR and phospho-mTOR), oxidative stress markers (malondialdehyde and protein carbonyls) and hippocampal neurogenesis, such as brain-derived neurotrophic factor (BDNF), phosphorylated extracellular signal-related kinase (p-ERK), and phosphorylated cyclic AMP response element binding protein (p-CREB). Notably,

AD mice receiving hiPSC-NSC-EVs displayed diminished mTOR signaling, evident from reduced pS6 expression and diminished phospho-mTOR concentration, lower oxidative stress markers, and enhanced autophagy apparent from reduced p62 expression. Moreover, hiPSC-NSC-EVs-treated mice exhibited improved hippocampal neurogenesis, evident from the higher numbers of doublecortin+ newly born neurons. Furthermore, BDNF, p-ERK, and p-CREB concentrations were higher in the hippocampus of AD mice receiving hiPSC-NSC-EVs than in AD mice receiving vehicle treatment. Collectively, the results suggest that intranasal administrations of hiPSC-NSC-EVs in the early stage of AD can effectively alleviate mTOR signaling and oxidative stress, enhance autophagy, and maintain higher levels of hippocampal neurogenesis by stimulating BDNF-ERK-CREB signaling.

Disclosures: S. Kotian: None. **L.N. Madhu:** None. **R. Upadhya:** None. **S. Rao:** None. **S. Attaluri:** None. **Y. Somayaji:** None. **B. Shuai:** None. **A.K. Shetty:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.19/B125

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

Support: NIH Grant 1RF1AG074256-01A1

Title: Intranasal hiPSC-NSC-EVs Treatment Slows Down Neuroinflammation and Cognitive Decline in Humanized APP Knock-in Mice, a Model of Late-Onset Alzheimer's Disease

Authors: *Y. SOMAYAJI[1], G. SHANKAR[2], V. RAO[2], S. RAO[2], L. N. MADHU[2], C. M. GOMEZ-GARCIA[3], J. PATEL[3], S. ATTALURI[2], B. SHUAI[2], X. RAO[2], A. K. SHETTY[4]; [1]Dept. of Genet. and Cell Biol.,, Inst. for Regenerative Med., Texas A& M Sch. of Med.,, College Station, TX; [2]Dept. of Genet. and Cell Biol.,, Inst. for Regenerative Med., Texas A&M Sch. of Med., College Station, TX; [3]Texas A&M Univ., College Station, TX; [4]Dept. of Cell Biol. and Genet., Inst. for Regenerative Med., Texas A&M Sch. of Med., College Station, TX

Abstract: Extracellular Vesicles (EVs) that are released by neural stem cells (NSCs) derived from human induced pluripotent stem cells (hiPSCs) contain miRNAs and proteins capable of promoting anti-inflammatory effects, autophagy and hippocampal neurogenesis. Hence, these EVs appear ideal for slowing the progression of Alzheimer's disease (AD). To test the efficacy of hiPSC-NSC-EVs in maintaining better cognitive function, we administered either vehicle or hiPSC-NSC-EVs (30 billion/dose) intranasally to 15-month-old mice with late-onset AD (human Aβ-loxP-knock-in B6.SJL-Apptm1.1Aduci/J [APP-KI] mice) every two weeks for two months. These mice already displayed cognitive and mood impairments at this point. The animals in both groups were subjected to a battery of neurobehavioral tests at 18 months, and brain tissues were processed at 20 months. The animals in both groups received 5-bromodeoxyuridine (BrdU; 100mg/kg/day) injections for 12 days, commencing a week after the last dose of vehicle/EVs to

quantify the extent of hippocampal neurogenesis. Tracking of PKH26-labeled EVs demonstrated that intranasally administered EVs were internalized by neurons and microglia in all brain regions. Compared to mice that received vehicle treatment, APP-KI mice that received hiPSC-NSC-EVs showed improvement in associative recognition and object location memories in object-in-place and object location tests. The hiPSC-NSC-EVs treated mice also showed better pattern separation and temporal pattern processing (TPP) ability in pattern separation and TPP tasks. They also did not display anhedonia in a sucrose preference test. Dual/triple immunofluorescence studies revealed that hiPSC-NSC-EVs treated APP-KI mice had reduced NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome complexes within microglia, reduced mechanistic target of rapamycin (mTOR) signaling (pS6 expression), and increased autophagy (p62 expression) within neurons of the hippocampus. Further validation of these changes via measurement of proteins or genes linked to NLRP3 inflammasome activation and its downstream inflammatory cascades, mTOR signaling, and autophagy is underway. Additionally, hiPSC-NSC-EVs treated APP-KI mice exhibited increased numbers of BrdU+ newly born cells and doublecortin+ newly born neurons in the hippocampus, quantifying which are in progress. The findings suggest that administering hiPSC-NSC-EVs intranasally after the onset of cognitive and mood impairments can limit the progression of neuroinflammation and mTOR signaling, improve autophagy, neurogenesis, and cognitive and mood function in a model of late-onset AD.

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Poster

PSTR328: Mouse Model Strategies for Alzheimer’s Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.20/B126

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

Support: This work is supported by a grant from the National Institutes for Aging (1RF1AG074256-01A1 to A.K.S.)

Title: Extracellular Vesicles from hiPSC-NSCs Can Alleviate Cognitive and Mood Dysfunction, Microgliosis and NLRP3 Inflammasomes in Tau P301S Mouse Model

Authors: *V. RAO, M. KODALI, Y. SOMAYAJI, S. ATTALURI, R. S. BABU, E. NARVEKAR, L. N. MADHU, X. RAO, B. SHUAI, S. RAO, G. SHANKAR, A. K. SHETTY; Inst. for Regenerative Med., Dept. of Cell Biol. and Genet., Sch. of Med., Texas A & M Univ., College Station, TX

Abstract: Alzheimer's disease (AD) is typified by an excess of phosphorylated tau protein in neurons. One of the neuropathological characteristics of AD, neurofibrillary tangles (NFTs),

composed of phosphorylated and misfolded tau, have been linked to cognitive impairments, progressive neuronal dysfunction, and neurodegeneration. Extracellular vesicles (EVs) released by human-induced pluripotent stem cell-derived neural stem cells (hiPSC-NSCs) are naturally enriched with miRNAs and proteins capable of mediating antiinflammatory properties. The administration of such EVs has improved cognitive and mood function in several neurodegenerative disease models exhibiting significant neuroinflammation. We investigated the efficacy of intermittent administrations of hiPSC-NSC-EVs for maintaining better cognitive and mood function in tau P301S mice (PS19, Strain #008169), a model of tauopathy and AD. Three-month-old female PS19 mice received intranasal administrations of vehicle or hiPSC-NSC-EVs once every two weeks over eight weeks (15 billion EVs/dose). In both groups, neurobehavioral tests were conducted to determine cognitive and mood function at the age of 5.5 months. Compared to age-match naïve control mice, untreated PS19 mice exhibited cognitive dysfunction, evident from impaired object location and object recognition memories in novel object recognition and object location tests, loss of pattern separation, and temporal pattern processing abilities in pattern separation and temporal pattern processing tasks. Notably, hiPSC-NSC-EVs treated PS19 mice displayed a much-improved ability for making objection location and recognition memories, pattern separation, and temporal pattern processing compared to untreated PS19 mice. Additionally, unlike untreated PS19 mice, PS19 mice receiving hiPSC-NSC-EVs did not display anhedonia in a sucrose preference test. Immunohistochemical and immunofluorescence analyses of brain tissues revealed significant microgliosis and increased percentages of microglia displaying NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome complexes in untreated PS19 mice. However, both microgliosis and microglia presenting NLRP3 inflammasome complexes were reduced in PS19 mice receiving multiple hiPSC-NSC-EVs treatment. Quantifying the effects of hiPSC-NSC-EVs on hippocampal neurogenesis and p-tau levels is underway. The results suggest that intermittent intranasal administrations of hiPSC-NSC-EVs in PS19 mice can postpone cognitive and mood impairments associated with the suppression of neuroinflammation.

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Poster

PSTR328: Mouse Model Strategies for Alzheimer’s Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.21/B127

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

Support: NIH grant R01AG057767
NIH grant R01AG061937
Smith Alzheimer’s Center
Kenneth Stark Endowment

Title: Sex-dependent cognitive and metabolic senolytic effects in an Alzheimer's model

Authors: Y. FANG[1], K. QUINN[1], M. PECK[1], T. HILL[1], J. CHAPMAN[1], A. BARTKE[2], K. N. HASCUP[1], *E. R. HASCUP[3];
[1]Dale and Deborah Smith Ctr. for Alzheimer's Res. and Treatment, [2]Intrnl. Med., [3]Southern Illinois Univ. Sch. of Med., Springfield, IL

Abstract: Senescent cells contribute to functional alterations associated with aging and neurodegenerative diseases including Alzheimer's disease (AD). A causal link has been shown between the accumulation of senescent cells and cognition-associated neuronal loss. Senolytic treatment in aged mice and mouse models of AD at advanced stages clears senescent cell burden leading to functional improvements. However, less is known regarding the effects of these compounds when administered prior to significant senescent cell accumulation or disease pathology. Here, we examine the effects of chronic intermittent senolytic treatments in young C57BL/6 (background control) and the APP^{NL-F} knock-in mouse model of AD. Male and female mice received monthly oral administration of Fisetin (100 mg/Kg BW), Dasatinib (5 mg/Kg BW) plus Quercetin (50 mg/Kg BW) (D+Q), or vehicle control starting at 4 months of age. All mice underwent glucose tolerance test (GTT) and insulin tolerance test (ITT) to examine glucose metabolism, indirect calorimetry to determine energy metabolism, and Morris water maze (MWM) and novel object recognition (NOR) to assess cognition. The results support that the senolytic treatment in young adulthood has beneficial, negligible, or detrimental effects in C57BL/6 or APP^{NL-F} mice dependent upon sex and genotype. Fisetin treatment had beneficial effects on male C57BL/6 mice by reducing adiposity, white adipose tissue (WAT), senescent markers, while improving glucose, energy metabolism, and memory. D+Q treatment led to detrimental effects in female C57BL/6 mice by increasing adiposity and WAT senescent markers. Unlike in C57BL/6, Fisetin treatment had negligible effects on both male and female APP^{NL-F} mice. D+Q treatment had beneficial impacts on female APP^{NL-F} mice by reducing adiposity, blood glucose, triglycerides, WAT and hippocampal senescent markers, soluble and insoluble Aβ42, and SA-β-gal activity in hippocampus. Collectively, this data reveals shared traits among senolytic treatments, supporting a connected relationship between peripheral energy metabolism and adiposity. This connection may influence cerebral mechanisms, thereby enhancing cognition in both normal physiological aging or Alzheimer's disease progression. This work was supported by the NIH (R01AG057767, R01AG061937), Smith Alzheimer's Center, and Kenneth Stark Endowment.

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Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.22/B128

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

Support: NIA R01AG057767
NIA R01AG061937
Dale and Deborah Smith Center for Alzheimer's Research and Treatment
Kenneth Stark Endowment
Illinois Department of Public Health 03282005H
Illinois Health Improvement Association
Geriatrics Research Initiative

Title: Sexually dimorphic effects of thermotherapy on metabolism and cognition in APP/PS1 mice

Authors: *M. R. PECK[1], E. D. IKIZ[1], K. QUINN[1], Y. FANG[1], A. BARTKE[2,3], E. R. HASCUP[1,4], K. N. HASCUP[1,3,4];
[1]Dept. of Neurology, Smith Alzheimer's Ctr., [2]Dept. of Intrnl. Med., [3]Dept. of Med. Microbiology, Immunol. and Cell Biol., [4]Dept. of Pharmacol., Southern Illinois Univ. Sch. of Med., Springfield, IL

Abstract: Current disease modifying monoclonal antibody treatments for Alzheimer's disease (AD) are often accompanied by severe side effects and high costs. As such, non-pharmacological treatments and lifestyle modifications may be a good alternative or option for combination intervention. Passive heat therapy has been shown to improve measures of cardiovascular function and glucose metabolism in non-demented individuals, which may translate to reduced risk of dementia and AD later in life. In this study, we aimed to investigate thermotherapy as a possible method of non-pharmacological management of symptoms relating to AD. We hypothesized that thermotherapeutic elevation of core body temperature (Tc) would result in improved metabolism and cognition in the APP/PS1 mouse model of AD. To test this hypothesis, we chronically exposed 6-month-old male and female APP/PS1 and C57BL/6 mice to 23 or 30°C for a period of 6 months. At 12 months of age, we conducted insulin and glucose tolerance tests and the Morris water maze to assess glucose metabolism and cognition, respectively. To further investigate the mechanisms behind the observed thermotherapeutic effects, we conducted plasma analysis and RT-PCR of adipose, liver, and skeletal muscle tissues, and assayed hippocampal tissue for amyloid concentration. Thermotherapy increased Tc in all groups except for female APP/PS1 mice, and we observed sexually dimorphic effects on both metabolism and cognition. In males, altered plasma hormone signaling and elevated glucose transporter 4 expression in skeletal muscle after thermotherapy resulted in improved glucose tolerance in both genotypes. While females also exhibited improvements in glucose metabolism, these changes were limited to C57BL/6 mice and were primarily a result of differing levels of metabolic regulatory and inflammatory gene expression in peripheral tissues. Thermotherapy improved spatial memory recall in both genotypes of male mice, but worsened long-term recall in female APP/PS1 mice. The improved cognition in APP/PS1 males was likely due in part to a reduction of hippocampal soluble $A\beta_{42}$ concentration. In female APP/PS1 mice, unchanged hippocampal soluble $A\beta_{42}$ concentrations coupled with elevated proinflammatory cytokine expression could explain the lack of cognitive improvement. In all, our findings support that thermotherapy should be explored as a beneficial treatment option for specific individuals with AD. These results also emphasize a need for further research into sex differences in AD pathology and treatment.

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Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.23/B129

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

Support: National Institute on Aging

Title: Alzped: an open science tool to increase rigor in therapeutic efficacy testing in alzheimer's animal models

Authors: *J. VISWANATHAN, M. LANFRANCO GALLOFRE, Z. MARTIN, S. PETANCESKA, S. CHAKROBORTY, L. REFOLO;
Natl. Inst. on Aging, Bethesda, MD

Abstract: Background: Positive findings from testing therapeutics in Alzheimer's disease (AD) animal models are frequently not translated to effective treatments due to the poor methodological rigor and inadequate reporting practices of therapeutic efficacy studies. NIA's Alzheimer's Disease Preclinical Efficacy Database (AlzPED) is a searchable and publicly available knowledgebase that prioritizes and promotes the use of rigorous methodology to ameliorate this translation gap in AD therapy development. Through a checklist of experimental design elements - the Rigor Report Card - AlzPED highlights reporting recommendations and standards while providing a practical tool that enables the planning of rigorous therapeutic studies in animals. AlzPED also serves as a platform for reporting negative findings to mitigate the publication bias favoring positive reports. **Methods:** Key word-driven literature searches are used to acquire and curate published studies. Two expert curators extract bibliographic details, funding source, study goals and principal findings, data on relevant translational criteria like therapy type, therapeutic agent, therapeutic target, animal models, and AD-related outcome measures, prior to publication in AlzPED. Rigor in study design and methodology is evaluated with the Rigor Report Card. All analytics including reports from negative findings are shared on AlzPED under the principles of open science. **Result:** AlzPED hosts curated summaries from over 1400 published preclinical therapeutic studies in AD animal models, data related to 274 therapeutic targets, 1201 therapeutic agents, 226 animal models, more than 3000 AD-related outcome measures, and thousands of principal findings. Evaluation of Rigor Report Cards demonstrates significant under-reporting of critical elements of methodology such as power/sample size calculation, blinding, randomization, balancing for sex, inclusion/exclusion criteria, these being reported by fewer than 35% of the 1400 curated studies. These deficiencies in reporting critical elements of methodology diminish the scientific rigor, reproducibility, and translational value of preclinical studies. **Conclusion:** Rigorous experimental design and transparent reporting are essential to inform future research, science policies, and successful

clinical trials. Adopting a standardized set of best practices like those proposed by AlzPED can improve the predictive power of preclinical studies in AD animal models and promote the effective translation of drug testing data to the clinic.

Disclosures: J. Viswanathan: None. **M. Lanfranco Gallofre:** None. **Z. Martin:** None. **S. Petanceska:** None. **S. Chakroborty:** None. **L. Refolo:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.24/B130

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

Support: NIH Grant GM146257
NIH Grant OD031672
The Wooten Foundation
The SmartState Endowment

Title: Spatial and rostral-caudal plane based profiling of RhoA/Rac1/Cdc42 activity status in the brain of 3xTg-AD mouse model of Alzheimer's disease

Authors: S. NIK AKHTAR[1], T. D. TRAN[2], ***Q. LU**[3];
[1]Chem. and Biochem., The Univ. of South Carolina, Columbia, SC; [2]Psychology, East Carolina Univ. Multidisciplinary Studies Program In Neurosci., Greenville, NC; [3]The Univ. of South Carolina, Columbia, SC

Abstract: Background: Small GTPases are critical for maintaining neuronal integrity. Neural synaptic loss in specific brain regions, such as the hippocampus and cortex, is one of the pathognomonic features of Alzheimer's Disease (AD). Small GTPases, such as RhoA, Rac1, and Cdc42, are dysregulated in AD brains. However, the exact contribution of their signaling to AD remains elusive. **Objective:** To shed light on the signaling contribution of RhoA, Rac1, and Cdc42 to AD pathophysiology we investigated the hypothesis that RhoA/Rac1/Cdc42 *activity* is dependent on the stereotactic plane and spatial dimensions of specific brain regions in AD-affected brains. **Methods:** For this study, we used brains from triple transgenic mouse model (3xTg-AD) possessing mutations in the amyloid precursor protein (APPswe), microtubule-associated protein tau (Tau) P301L, and presenilin1 (PS1) M146V. We performed immunohistochemical analysis using antibodies against pRhoA, pRac1/Cdc42, pPAK, and pLIMK. Anti-pRhoA recognizes an inactive state of RhoA (S188 phosphorylation); anti-pRac1/Cdc42 (Serine 71 phosphorylation) reacts with an inactive state of Rac1/Cdc42; anti-pPAK (Threonine 423 phosphorylation) detects the active PAK, a positive downstream effector of Rac1/Cdc42 signaling; and anti-pLIMK (T508 phosphorylation) recognizes an active state of LIMK (T508 phosphorylation), a downstream effector of RhoA. **Results:** pRhoA expression increased in the cortex whereas pRac1/Cdc42 decreased in the cortex of the 3xTg-AD mouse

brain. pLIMK and pPAK expressions were oppositely correlated with pRhoA and pRac1/Cdc42 expression in the cortex of 3xTg-AD mice, respectively. Rostral-caudal-based immunohistochemical profiling of WT mouse brain serial sections revealed increased pRac1/Cdc42 and decreased pRhoA expression in the rostral regions of the brain, and opposite staining profiles in the caudal regions of the brain. pPAK and pLIMK showed an overall opposite trend to pRac1/Cdc42 and pRhoA along the rostral-caudal dimensions, respectively. There was also a brain plane-specific nuclear to cytoplasmic redistribution of both pRac1/Cdc42 and pRhoA. Mouse whole transcriptome analysis demonstrated spatial dependent expression of Rho-GTPase signaling-associated genes in neuronal (Neun Positive) and astrocyte (GFAP positive) populations of 3xTg-AD hippocampi. **Conclusion:** RhoA/Rac1/Cdc42 activity status is dysregulated in 3xTg-AD mice and changes along the rostral-caudal and spatial dimensions. Supported by NIHR01NIGMS146257 (R01OD031672), The Wooten Foundation

Disclosures: S. Nik AKhtar: None. **T.D. Tran:** None. **Q. Lu:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.25/B131

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

Support: NIH-NIA U01 AG066722

Title: The highly selective serotonin 5-HT_{2b}receptor antagonist MW073 attenuates synaptic and behavioral dysfunction in mouse models of tau and amyloid-beta elevation.

Authors: *O. ARANCIO[1], E. ACQUARONE[1], E. K. ARGYROUSI[1], H. ZHANG[1], A. STANISZEWSKI[1], J. J. ZIAREK[2], S. M. ROY[2], D. WATTERSON[2];
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Abstract: Neuropsychiatric syndromes such as anxiety, depression, and agitation are clinical presentations across the life span, but are critical patient and public health issues in diverse neurodegenerative diseases, neurodevelopment complications, and brain injury sequalae. These syndromes impact cognition, making them a critical health and quality of life concern. Further, patient presentation of neuropsychiatric disturbances routinely precedes or emerges coincident with clinical biomarkers or severe cognitive decline. For example, early pathologies of Alzheimer's disease related disorder (ADRD) include the loss of serotonin (5-hydroxytryptamine; 5-HT) neurons in the raphe nucleus and appearance of neurofibrillary tangles in the dorsal raphe nucleus, a region rich in 5-HT neurons. The resultant pathophysiology can be diverse and increase with progression based on 5-HT modulatory role in neuropsychological and cognitive function, which are often associated with serotonin receptors 5-HT_{2a}R and 5-HT_{2b}R. Further, our discovery of increased 5-HT_{2b}R levels in AD patient brains vs age-matched controls (Acquarone et al, 2024) is consistent with the hypothesis that 5-HT_{2b}R

inhibition might be beneficial in ADRD. We therefore developed a highly selective 5-HT_{2b}R antagonist, MW073, using strategic optimization that, like drug repurposing, leverages the clinical and pharmacological portfolio of an existing drug but allows enhancement of desired functions with coincident removal clinical risks inherent to the existing clinical drug. MW073 is strategically optimized analog of the atypical neuroleptic drug cantor, which exhibited low risk for cardiotoxicity, drowsiness, or weight gain in neurology patients and was found to enhance cognitive and behavioral improvement in a 122 AD patient, double-blind, placebo-controlled, multi-center, proof-of-concept clinical trial. MW073 treatment of AD animal models attenuated tau- and amyloid-induced impairments of associative and spatial memory as measured through freezing during fear conditioning and number of errors in the radial-arm-water-maze test. MW073 also prevented amyloid and tau induced LTP defects in hippocampal slices challenged with Aβ or tau-oligomers. Efficacy was observed with administration in both “prevention mode” and “disease state mode”. In conclusion, MW073 efficacy and pharmacodynamic effects *in vivo* are consistent with its potential future utility in attenuating tau- or amyloid-induced pathophysiology and suggests the broader potential of strategic optimization of atypical neuroleptic clinical drugs for treatment of neuropsychiatric syndromes.

Disclosures: O. Arancio: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurokine Therapeutics. **E. Acquarone:** None. **E.K. Argyrousi:** None. **H. Zhang:** None. **A. Staniszewski:** None. **J.J. Ziarek:** None. **S.M. Roy:** None. **D. Watterson:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer’s Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.26/B132

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

Support: Stanley E. Fulton Foundation

Title: Prophylactic administration of memantine provides disease-modifying properties in Alzheimer's disease and pure tauopathy model mice

Authors: A. F. SILVA[1], A. E. WASSERMAN[1], D. BIGLER WANG[2], T. KIM[1], M. A. JANSEN[1], J. GATESMAN[3], I. S. MAULDIN[4], S. S. BERR[5], *G. S. BLOOM[1];
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Abstract: There are now more than 55 million humans with Alzheimer's disease (AD), with a possible increase to more than 78 million by 2030. The FDA has approved 2 monoclonal antibodies (Aduhelm and Leqembi), 3 cholinesterase inhibitors (donepezil, rivastigmine and

galantamine), an NMDA receptor antagonist (memantine) and a 2 drug cocktail (donepezil and memantine) to treat AD, but none of these therapies have been tested for AD prevention.Our lab has shown that ectopic neuronal cell cycle re-entry, which may lead to 90% of neuron death in AD and is a seminal pathogenic process, can be prevented by memantine in Aβ oligomer-treated cultured neurons and Tg2576 AD model mice (https://doi.org/10.1016/j.jalz.2018.05.017). Those results raised the possibility that memantine has previously unrecognized disease-modifying properties that can be harnessed prophylactically for AD, and other tauopathies. To test that hypothesis, we compared effects of treating AD (J20) and pure tauopathy (hTau) mice with memantine, beginning either before learning and memory deficits occur (early), or when they appear (late). J20, hTau and wild type (WT) mice had *ad libitum* access to memantine in drinking water. Early treatments began at 5 weeks for all strains, and late treatments began at 4 and 6 months, respectively, for J20 and hTau mice. Treatment of WT mice began only at 5 weeks, and untreated animals of all strains served as controls. All animals were periodically evaluated by Morris water maze (MWM), novel object recognition (NOR), amyloid PET (J20 only), MRI and immunohistochemistry. Baseline MWM and NOR performances were indistinguishable by strain. At 18 months, though, all mice treated early had improved MWM performances compared to untreated or late treated mice of the same strain, including the WT mice. NOR performance at 18 months was similarly protected for early treated J20s. PET imaging and immunofluorescence at 18 months indicated that early treatment of J20s caused an ~40% reduction in plaques compared to late treated and untreated J20s, which were indistinguishable from each other at that time point. When administered prophylactically to AD and pure tauopathy mice, but not when treatment began at symptom onset, memantine thus had disease-modifying properties by both behavioral and histopathological criteria. Remarkably, the WT mouse results suggest that memantine can also reduce normal, age-dependent cognitive decline. These results justify an effort to re-purpose memantine from its current use as a modest and temporary symptom relieving drug for moderate to severe AD to a prophylactic that might prevent or delay symptom onset, and in the latter case, slow disease progression.

Disclosures: A.F. Silva: None. **A.E. Wasserman:** None. **D. Bigler Wang:** None. **T. Kim:** None. **M.A. Jansen:** None. **J. Gatesman:** None. **I.S. Mauldin:** None. **S.S. Berr:** None. **G.S. Bloom:** None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.27/B133

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

Support: R01 NS077239
R01 AG032611

Title: Neuronal uptake and efficacy of tau antibodies is mediated by Fcγ receptors

Authors: *E. CONGDON[1], Y. LIN[1], E. M. SIGURDSSON[1,2];
[1]Dept. of Neurosci. and Physiol. and Neurosci. Inst., New York Univ. Grossman Sch. of Med., New York, NY; [2]Department of Psychiatry, New York University Grossman School of Medicine, New York, NY

Abstract: While immunotherapy remains a promising strategy for tauopathies, several antibodies that target extracellular tau have failed in clinical trials. Because >99% of tau pathology is intracellular, we argue that antibodies must target this intracellular pool. Importantly, we showed that inhibiting Fc receptor-mediated endocytosis reduced tau antibody efficacy (Congdon et al. 2013, JBC). However, others argue that uptake into neurons is unnecessary (Congdon et al. 2023, Nat Rev Neurol). For a definitive answer, we obtained a mouse model lacking all Fcγ receptor expression (Casey et al. 2018, Leukemia), and used them to generate neuronal cultures. Cultures from wild type (WT) and FcγKO mice were incubated with 4E6, an antibody we developed that recognizes the pSer396/404 tau epitope, and is efficacious in cell and animal models (Congdon et al. 2023, Nat Rev Neurol). Neuronal uptake was assessed using live cell imaging. FcγKO neurons had significantly lower levels of internalized 4E6 (95% reduction, $p < 0.0001$), but were able to internalize 10 kDa dextran, indicating that the cells were capable of bulk endocytosis. Subsequently, primary neurons prepared from FcγKO pups were treated with human paired helical filament (PHF) tau and 4E6 using dosing paradigms that simulate extra- and intracellular tau binding. In the extracellular paradigm, PHF alone induced significant toxicity and tau seeding (33% decrease in NeuN, Tau/NeuN ratio 6.9, $p < 0.0001$ for both), and 4E6 blocked these effects ($p < 0.0001$ relative to PHF alone). In the intracellular paradigm, PHF alone again induced pathology (41% decrease in NeuN, Tau/NeuN ratio 6.6, $p < 0.0001$ for both). However, when the PHF was inside the neurons, 4E6 was ineffective in preventing its pathological effects, showing the importance of FcγR-mediated uptake. We then crossed the FcγKO line with PS19 mice, which express mutant human P301S tau. Animals were given an i.v. injection of a fluorescently labeled tau antibody that was detected using the In Vivo Imaging System. In past experiments, tauopathy mice showed higher tau antibody uptake compared to WT animals from the same background, and that uptake correlated highly with tau pathology. In contrast, the FcγKO/PS19 mice did not show enhanced uptake compared with the FcγKO littermates, and peak signal did not correlate with tau levels. These results show that tau antibody uptake into neurons and its efficacy in neutralizing and clearing pathological tau are mediated by FcγR . These findings have important implications for the design of therapeutic tau antibodies, namely that optimal efficacy requires Fc binding and neuronal uptake.

Disclosures: E. Congdon: None. **Y. Lin:** None. **E.M. Sigurdsson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EMS is an inventor on patents on tau immunotherapies and related diagnostics that are assigned to New York University.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.28/B134

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

Support: Alzheimer's Association Grant AARG-D-615714
Alzheimer's Association Blas Frangione Early Career Achievement Award
Serrapilheira Institute Grant R-2012-37967
CNPq grant 309728/2022-8
FAPERJ grant 210.316/2022

Title: Targeting brain translational control to improve memory and depressive-like states in mice

Authors: *M. V. LOURENCO;
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Abstract: Major depressive disorder (MDD) is a significant cause of disability in adults worldwide. However, the underlying causes and mechanisms of MDD are not fully understood. Impaired control of brain mRNA translation underlies several neurological conditions, including autism spectrum disorders and Alzheimer's disease (AD). We showed that restoring proper brain translation rates prevents memory impairment in AD mouse models. Nonetheless, a potential role for impaired translational control in depressive-like behavior remains elusive. A key pathway controlling translation initiation relies on the phosphorylation of the α subunit of eukaryotic initiation factor 2 (eIF2α-P) which, in turn, blocks the guanine exchange factor activity of eIF2B, thereby reducing global translation rates. Here we report that the expression of EIF2B5 (which codes for eIF2B epsilon, the catalytic subunit of eIF2B) isreduced in in postmortem MDD prefrontal cortex from two distinct human cohorts and in the frontal cortex of social isolation-induced depressive-like behavior model mice. Further, pharmacological repression of brain protein synthesis by treatment with anisomycin or with salubrinal, an inhibitor of the eIF2α phosphatase GADD34, induces depressive-like behavior in adult C57BL/6J mice. Salubrinal-induced depressive-like behavior is blocked by ISRIB, a compound that directly activates eIF2B regardless of the phosphorylation status of eIF2α, suggesting that the impact of eIF2α-P on translation promotes depressive-like states. Taken together, our results suggest that impaired mRNA translation participates in the pathophysiology of MDD, and underscore eIF2-linked translational control as a potential target for novel therapeutics in MDD.

Disclosures: M.V. Lourenco: None.

Poster

PSTR328: Mouse Model Strategies for Alzheimer's Disease II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR328.29/B135

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

Support: NIH-NS108189

Title: Provisional evidence that selective activation of mTOR in neurons that degenerate in 5xFAD mice delays age-related neurodegeneration

Authors: *D. GALLARDO[1], O. STEWARD[2];
[1]Anat. and Neurobio., Univ. of California, Irvine, Irvine, CA; [2]Anat. and Neurobio.; Neurobio. and Behavior; Reeve-Irvine Res. Ctr., Univ. of California, Irvine, Irvine, CA

Abstract: Neurodegeneration is a primary driver of cognitive decline and functional impairment in Alzheimer's disease (AD). Defining mechanisms of neurodegeneration and identifying neuroprotective interventions may reveal novel therapeutic targets. As neurodegeneration is age-related, reverting neurons to a growth state similar to that in early development, could delay or prevent neuronal death. Our lab has previously found that activation of the AKT/Mechanistic target of rapamycin (mTOR) pathway via PTEN deletion transforms neurons to a growth state (Gallent et al., 2018). To assess whether PTEN deletion in neurons that degenerate might be neuroprotective, we created triple transgenic mice by crossing 5XFAD mice with $PTEN^{f/f}/Rosa^{tdTomato\ (tdT)}$ reporter mice in which exon 5 of the Phosphatase Tensin Homolog (PTEN) gene is flanked by lox-P sites ($PTEN^{f/f}$) and a lox-P flanked STOP cassette is in the Rosa26 locus upstream of a tdT fluorescent protein sequence ($5XFAD/PTEN^{f/f}/Rosa^{tdT}$). To selectively delete PTEN in one population of neurons that degenerate (pyramidal neurons in cortical layer V) we used a novel variant of Adeno-associated Virus (AAV) that transports cargo retrogradely, AAV-retrograde (AAV-rg). Injections of AAV-rg/Cre into the spinal cord lead to retrograde transduction of layer V neurons that project to the spinal cord, resulting in PTEN deletion and activation of tdT expression. Permanent labeling of cell bodies, axons and dendrites of PTEN-deleted layer V neurons provides a way to track neurodegeneration across age and assess whether persistent activation of mTOR via PTEN deletion is neuroprotective. Male and female $5xFAD/PTEN^{f/f}/Rosa^{tdT}$, and control $5xFAD/Rosa^{tdT}$ mice received intra-spinal cord injections of AAV-rg/Cre at 4 months old; mice were euthanized between 5-15 months old to track neurodegeneration. In $5xFAD/Rosa^{tdT}$ mice, early signs of degeneration of tdT-labeled layer V neurons included development of large axonal swellings and fragmentation and dendritic dystrophy. An unexpected feature was the appearance of tdT-positive extracellular debris in cortical layer VI and below, which co-localized with accumulations of Aß. TdT-positive extracellular debris was already present at 5 months of age. Preliminary quantitative comparisons of mice 5, 8 and 12 months of age revealed a greater survival of neurons in $5xFAD/PTEN^{f/f}/Rosa^{tdT}$ compared to $5xFAD/Rosa^{tdT}$ controls and less extracellular tdT-positive debris. These preliminary data support the provisional conclusion that selective activation of mTOR delays age-related neurodegeneration in 5XFAD mice.

Disclosures: D. Gallardo: None. **O. Steward:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-founder, scientific advisor, and has economic interests in the company Axonis Inc, which is developing novel therapies for spinal cord injury and other neurological disorders.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.01/B136

Topic: C.03. Parkinson's Disease

Title: Impact of pathological alpha-synuclein brain spread on motor behavior, electroencephalography (EEG), Auditory-event related potential (AERP) and auditory-steady state response (ASSR) in mice injected with pre-formed α-synuclein fibrils (PFFs).

Authors: *A. MICHEL[1], V. DUVEAU[2], G. MAIRET COELLO[1], F. HUSTADT[1], C. DE WOLF[1], C. ROUCARD[2];
[1]UCB Biopharma, Braine l'Alleud, Belgium; [2]Synapcell SAS, St Ismier, France

Abstract: The gradual spread of intracellular inclusions of pathological α-synuclein into the brain is considered as the major neuropathological feature supporting the progression of Parkinson's disease (PD). The propagation of α-synuclein leads to synaptic dysfunction and loss, as well as disrupted dendritic spine remodeling. Consequently, demonstrating whether the spreading of α-synuclein aggregates can correlate with changes in the brain EEG activity of mice injected with PFFs could be of great value for monitoring disease progression. This observation would be particularly interesting since it is difficult to identify a progressive, reproducible motor deficit in this mouse model. C57Bl/6J mice were bilaterally injected with either a vehicle or 5 µg of α-synuclein PFFs in both sides of the striatum. Behavioral characterization (general activity, pole test, rotarod, wire-hanging) was performed at 6 months post-injection (pi); resting EEG, Auditory Evoked Potential (AERP), and 40Hz-Auditory Steady States Response (40Hz-ASSR) were conducted at 7-8 months pi; brain collection occurred at 9 months pi. Mice were bilaterally implanted with four monopolar electrodes (two per hemisphere: one in the cortex and the second in the striatum). Three paradigms were performed over one week, and then repeated for confirmation: EEG on day 0, AERP on day 2, and ASSR on day 4. Behavioral phenotyping revealed no motor deficit in PFFs-injected mice compared to sham-treated ones. Similarly, resting EEG results from the motor cortex and striatum showed no difference between the two groups. The processing of sensory information was evaluated by measuring the AERP and 40Hz ASSR. No differences were observed between the sham and PFFs-injected mice. Despite the absence of changes in motor function, resting EEG, AERP, and 40Hz-ASSR in PFFs-treated mice, postmortem brain imaging analysis clearly showed that only mice injected with PFFs developed pathological pS129 α-synuclein aggregates in the striatum, cortex, and amygdala, confirming the development of the pathology. In conclusion, while the PFFs-treated mouse model is highly relevant for deciphering the biological mechanisms underlying the progressive spread of α-synuclein pathology across discrete brain areas, it is not adequate for monitoring disease progression in live animals. These results support the hypothesis that this model represents the very early forms of PD pathology that precede major neuronal degeneration and its functional consequences.

Disclosures: A. Michel: A. Employment/Salary (full or part-time):; UCB Biopharma. **V. Duveau:** A. Employment/Salary (full or part-time):; Synpapcell. **G. Mairet Coello:** A. Employment/Salary (full or part-time):; UCB Biopharma. **F. Hustadt:** A. Employment/Salary

(full or part-time):; UCB Biopharma. **C. De Wolf:** A. Employment/Salary (full or part-time):; UCB Biopharma. **C. Roucard:** A. Employment/Salary (full or part-time):; Synpapcell.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.02/B137

Topic: C.03. Parkinson's Disease

Support: APVV-20-0331
SASPRO 2_1085/01/02
ICGEB CRP/SVK22-04_EC

Title: Differential response of neuronal cell lines to alpha-synuclein alterations

Authors: *M. MOMAND[1], L. FIALOVÁ[1], K. ALBERTUSOVÁ[1], D. FRICOVA[2,3];
[1]Inst. of Neuroimmunology, Slovak Acad. of Sci., Bratislava, Slovakia; [2]The unit for translational Res. of neurodegenerative Dis., 2nd Neurol. Dept., Fac. of Med., Comenius Univ., Bratislava, Slovakia, Bratislava, Slovakia; [3]Institute of Neuroimmunology, Slovak Academy of Sciences, Bratislava, Slovakia

Abstract: Alpha-synuclein (a-Syn) has been identified as a primary component of the characteristic protein aggregates i.e. Lewy bodies (LBs) that accumulate in the Parkinson's disease (PD) brain. However, the precise molecular mechanisms that lead to the aggregation of this natively disordered protein in LBs and subsequent neurodegeneration remain unclear warranting the need for further studies, and the development of novel research tools. In our present study, we created novel cellular models of a-Syn induced toxicity in two distinct neuronal cell lines i.e. SH-SY5Y neuroblastoma cell line and ReNVM neural progenitor cell line, stably overexpressing GFP tagged a-Syn (both WT and PD-related mutant A53T) via lentivirus transduction. We then sorted these cell lines into subpopulations based on the expression of GFP to achieve dosage-dependent expression of a-Syn. We characterized these cell models for the levels of a-Syn and compared subpopulations among themselves, WT with A53T and cells based in SH-SY5Y with those based in ReNVM cells, followed by qualitative profiling of various a-Syn species e.g. phosphorylated or aggregated. We then studied the effects of altered a-Syn levels on cytotoxicity, reactive oxygen species (ROS) production, mitochondrial metabolism, and function. Our study revealed differences in cellular responses not only based on the levels and type of a-Syn (WT or A53T) but also between the two cell types i.e. SH-SY5Y and ReNVM showing that these cells respond differently to the alterations in a-Syn levels. Results from our study contribute to elucidating the intricate cellular processes underlying a-Syn-induced toxicity in PD and related disorders and could identify the cell type most suitable for the modeling of a-Syn-related pathologies in neurodegeneration.

Disclosures: M. Momand: None. **L. Fialová:** None. **K. Albertusová:** None. **D. Fricova:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.03/B138

Topic: C.03. Parkinson's Disease

Support: Pathway-to-Independence Award, MiND Program, VAn Andel Institute

Title: Pathology and neurodegeneration in an α-synuclein preformed fibril mouse model are independent of ATP13A2

Authors: *C. MASSARI[1], D. DUES[2], A. BERGSMA[2], D. J. MOORE[2];
[1]Van Andel Res. Inst., Grand rapids, MI; [2]Van Andel Inst., Grand Rapids, MI

Abstract: Loss-of-function mutations in *ATP13A2* (PARK9) are implicated in early-onset autosomal recessive Parkinson's disease (PD) and other neurodegenerative disorders. *ATP13A2* encodes a lysosomal transmembrane P5B-type ATPase that is highly expressed in brain and specifically the substantia nigra. Recent studies have revealed its role as a lysosomal polyamine transporter, although its contribution to PD-related pathology remains unclear. *In vitro* studies report that ATP13A2 regulates α-synuclein (α-syn) secretion via exosomes. However, in animal models, the relationship between ATP13A2 and α-syn remains inconclusive. *ATP13A2* knockout (KO) mice exhibit lysosomal abnormalities and reactive gliosis but do not develop PD-related neuropathology. Studies manipulating α-syn levels in mice lacking ATP13A2 show minimal effects on pathology. The delivery of α-syn preformed fibrils (PFFs) into the mouse striatum is a well-defined model to study the development and spread of α-syn and pathology. In this study we unilaterally injected wild-type (WT) and homozygous *ATP13A2* KO mice with mouse α-syn PFFs in the striatum and evaluated mice for pathology after 6 months. The distribution and spread of α-syn inclusions throughout the mouse brain was independent of ATP13A2 expression. The loss of nigrostriatal pathway dopaminergic neurons and their nerve terminals induced by PFFs were equivalent in WT and *ATP13A2* KO mice. Reactive astrogliosis was induced by α-syn PFFs in WT mice but was significantly higher in *ATP13A2* KO mice, however, this was due to pre-existing gliosis in the KO mice. We did not identify asymmetric motor disturbances, microglial activation, or axonal damage induced by α-syn PFFs in WT or KO mice. TH-positive neurons in the substantia nigra exhibit increased lysosomal LAMP2 levels induced by PFFs in WT mice, whereas *ATP13A2* KO mice already display enlarged lysosomes in general. Our study evaluating the spread of α-syn pathology reveals no exacerbation of α-syn pathology, neuronal loss or motor deficits in *ATP13A2* KO mice, suggesting that lysosomal ATP13A2 does not play a major role in α-syn clearance or propagation *in vivo*.

Disclosures: C. Massari: None. **D. Dues:** None. **A. Bergsma:** None. **D.J. Moore:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.04/B139

Topic: C.03. Parkinson's Disease

Title: Development of iPSC-based Parkinson's disease model for drug discovery

Authors: *C. FORMICA[1,2], B. SAMSON-COUTERIE[2], L. SMIT[2], A. DAS[2], I. ONOFRE[2], **S. JAIN**[2];
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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease, with a prevalence that doubled in the past decades and that is projected to double again in the future. However, the cause of the disease is not yet completely clear, and a definitive treatment is still missing. One major reason for this is the use of inappropriate preclinical models, which fail to recapitulate the myriad of pathological phenotypes associated with PD. Induced pluripotent stem cells (iPSCs) and, particularly, patient-specific iPSCs, represent a powerful tool to overcome many of the present shortcomings. Methods. Ncardia used iPSC-derived dopaminergic neurons (iPSC-DN) treated with SNCA recombinant pre-formed fibrils (PFFs) to model disease relevant phenotypes of PD. Using high content imaging, phosphorylated alpha synuclein (pS129 α-Syn) area, number of puncta and intensity were calculated. Additionally, Ncardia investigated the effect of α-Syn accumulation on autophagy and mitochondrial density and function. Finally, proteasomal activity and MEA activity were measured. Results. Treatment of iPSC-DN with PFFs resulted in a robust increase of phosphorylated α-Syn. This was accompanied with alteration of autophagy, decreased mitochondrial density and function and decreased proteasomal activity. Conclusions. Ncardia developed a series of assays to recapitulate the main PD hallmarks using human iPSC-derived neuronal cell models, providing clinically relevant readouts to support drug innovators at various stages of drug discovery, increasing confidence on their predictions and potentially reducing the need for laboratory animals.

Disclosures: C. Formica: A. Employment/Salary (full or part-time):; Ncardia Services BV. **B. Samson-Couterie:** A. Employment/Salary (full or part-time):; Ncardia Services BV. **L. Smit:** A. Employment/Salary (full or part-time):; Ncardia Services BV. **A. Das:** A. Employment/Salary (full or part-time):; Ncardia Services BV. **I. Onofre:** A. Employment/Salary (full or part-time):; Ncardia Services BV. **S. Jain:** A. Employment/Salary (full or part-time):; Ncardia Services BV.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.05/B140

Topic: C.03. Parkinson's Disease

Support: NIH Grant 1R21NS123512-01 (JEM)
University of Arizona Department of Neuroscience Hildebrand summer research fellowship award (FZP)

Title: The Silence Before the Storm: Understanding Early Mechanisms of Alpha-synuclein Proteinopathy in a Songbird Model of Vocal Dysfunction

Authors: *F. PATEL[1], R. BJORK[2], M. DALY[1], J. E. MILLER[3];
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Abstract: Parkinson's disease (PD), a neurodegenerative brain condition characterized by toxic aggregation of the alpha-synuclein (Asyn) protein, significantly impairs individuals' quality of life through movement and vocal deficits. Although extensive research has been conducted in rodent models of PD-related limb motor dysfunction, limited animal model studies to date have investigated the correlation between Asyn-driven subcellular pathologies and early vocal dysfunction in PD. Fortunately, songbirds offer an advantageous and highly relevant platform for such analyses, due to the fact that male zebra finches possess a well-characterized song-dedicated vocal circuit that is anatomically and genetically similar to human speech circuits. In our present study, we use an adeno-associated virus (AAV) containing the human *SNCA* gene to selectively overexpress human Asyn (hAsyn) in finch basal ganglia song center Area X. Controls received either no injection (naïve) or AAV injection containing green fluorescent protein (GFP). Our prior findings showed that hAsyn overexpression resulted in alterations in vocal features-namely, a reduction in pitch, amplitude and duration-at the single syllable level, mirroring the clinical deficits observed in human patients. The goal of this current study was to use immunohistochemistry to determine which feature(s) of Asyn pathology best correlates with vocal phenotype severity. We assessed regional and subcellular localization of Asyn protein and its Ser129 phosphorylation, neuritic swellings, and cell type specificity of the hAsyn transgene. Preliminary results suggest that hAsyn localizes predominantly in neuronal processes within Area X with Ser129-positive expression in cell bodies residing in upstream cortical song region, LMAN. Vocal analyses are underway. We predict that finches with Ser129-positive hAsyn expression in LMAN and/or a high level of aggregates in Area X neurites will exhibit more dramatic vocal deficits than finches expressing lower levels. Our results will inform how subcellular Asyn pathologies correlate with vocal deficits and will contribute to a better understanding of the human vocal neuropathology.

Disclosures: F. Patel: None. **R. Bjork:** None. **M. Daly:** None. **J.E. Miller:** F. Consulting Fees (e.g., advisory boards); Michael J. Fox Foundation for Parkinson's Research.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.06/B141

Topic: C.03. Parkinson's Disease

Support: Michael J Fox Foundation Project Grant No. 2019-008814

Title: The combined effects of tau seeds and Lewy bodies distant injections on nigral dopaminergic degeneration in non-human primates

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Abstract: In neurodegenerative diseases, co-pathologies' influence on the emergence of a clinical phenotype is increasingly acknowledged. Recently, it has been suggested that nigral tauopathy may contribute to the nigrostriatal degeneration characterising Parkinson's disease (PD) and Parkinsonism, either independently or in conjunction with Lewy body (LB) pathology. However, these conclusions are primarily based on post-mortem neuropathological correlations, and there is (yet) no direct experimental evidence to support this hypothesis. Here, we study the neuropathological impact of spreading these two proteinopathies toward the mesencephalon by injecting macaques (*Macaca mulatta*) with LB, tau aggregates, and a combination of LB and Tau aggregates.PD brain-derived LBs (PD-LB) were injected into the striatum of seven macaques. Alzheimer's disease (AD) brain-derived tau seeds (AD-tau) were injected into the thalamus, located above the mesencephalon, of fourmacaques. A third group of four macaques received the combination of PD-LB into the striatum and AD-tau into the thalamus. As a control procedure, we injected tau extracts from aged-matched healthy brains in three macaques. Eighteen months post-injections, stereological counting of tyrosine-hydroxylase (TH)-positive neurons in the substantia nigra revealed a significant dopaminergic neuronal loss ($p=0.021$) in LB-injected macaques (-26.5%), in macaques injected with AD-tau (-38.4%) and a much greater lesion in macaques co-injected with AD-tau and LBs (-53.5%). Our findings support that nigral dopaminergic neuronal death can be caused by the spreading of tau proteopathic seeds and α-synuclein-containing LB from rostral connected regions, with a cumulative effect of the co-pathology. Further investigations will aim to characterise the presence of tauopathy and synucleinopathy across various brain regions.

Disclosures: M. Darricau: None. **V. Kulifaj:** None. **W. Meissner:** None. **B. Dehay:** None. **E. Bezard:** A. Employment/Salary (full or part-time):; Motac. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac, TrEEFROG THERAPEUTICS, SE Therapeutics. **V. Planche:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.07/B142

Topic: C.03. Parkinson's Disease

Title: From literature identification to efficient validation of targets in vitro - effects on alpha-synuclein aggregation in cortical neurons

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Abstract: Insoluble aggregates (Lewy bodies) consisting of misfolded alpha-synuclein (αSyn) accumulate in the nervous system of most Parkinson's disease (PD) patients. This process can affect multiple cellular functions, eventually leading to neuronal death. In the current study, the aim was to identify and validate targets involved in modulation of αSyn aggregation using an in vitro model. Based on literature evidence, 20 targets were chosen for their potential involvement in αSyn aggregation pathways, such as regulation of αSyn expression, post-translational modifications, or autophagy/lysosomal degradation. Lentiviral shRNAs, were added to primary mouse embryonic (E18) cortical neurons one day after plating and αSyn aggregation was induced by addition of pre-formed fibrils (PFFs) 6 days later. Using an unbiased automated image analysis workflow, the effect of selected mRNAs on αSyn aggregation (assessed by phosphorylation of Ser129) was evaluated one or two weeks after PFF addition. In addition, cell health was evaluated. A hit analysis was performed using strictly standardized mean (SSMD) and a target was defined as a hit if SSMD was ≥1.5, effect on αSyn aggregation was ≥ 20% and cell health was ≥ 60%. Lentiviral shRNA-mediated downregulation of some targets caused effects on neuronal survival. However, as previously reported (PSTR016.06, SfN 2023), lentiviral shRNA treatment of some targets (Zscan21, Vps35 and Fyn resulted in an increased αSyn aggregation, whereas lentiviral shRNA treatment of some targets (e.g. Ppp1r15a, Rhot1 and Bach1) resulted in a decrease in αSyn aggregation without large effects on neuronal health. To further validate the findings, selected hits were confirmed by investigating knock-down of the target on gene expression level. We conclude that our in vitro model is useful for identification and validation of targets involved in modulation of αSyn aggregation. In addition, this model could be used for testing of compounds aimed for a specific target. We provide a list of potential targets for modulation of αSyn aggregation, which should be further investigated in αSyn aggregation models in human neurons and in vivo, aiming to develop disease-modifying therapies for PD.

Disclosures: L. Strid Orrhult: A. Employment/Salary (full or part-time):; Cellectricon AB. **A. Vuorenpää:** A. Employment/Salary (full or part-time):; Orion Corporation. **E. Rannikko:** A. Employment/Salary (full or part-time):; Orion Corporation. **P. Karila:** A. Employment/Salary (full or part-time):; Cellectricon AB. **A. Domanskyi:** A. Employment/Salary (full or part-time):; Orion Corporation. **J. Pihl:** A. Employment/Salary (full or part-time):; Cellectricon AB.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.08/C1

Topic: C.03. Parkinson's Disease

Title: Aav-human-a53t-mutated synuclein disrupts nigro-striatal system in mice

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Abstract: Phosphorylation and aggregation of α-synuclein (α-syn) plays a crucial role in Parkinson's disease (PD) and other neurodegenerative diseases. The A53T point mutation in α-syn, which has been identified in rare forms of familial PD, is reported to increase α-syn oligomerization and aggregation. Thus, we generated a mouse model recapitulating core features of PD that can be used to research A53T α-syn-related pathologies, downstream effects and ultimately be a valuable tool for the development of new therapeutics.
To this end, the substantia nigra (SN) of 13 weeks old C57BL/6J mice was unilaterally injected with AAV-human A53T mutated α-syn (AAV-hA53T). The contralateral SN was treated with an AAV-empty control vector. After 8 weeks, brains were collected and analyzed by biochemical and histological methods.
Analyses revealed that human α-syn levels were highly increased in the ipsilateral SN as determined using a Mesoscale Discovery (MSD) immunosorbent assay and quantitative immunofluorescence, suggesting that the α-syn expression driven by the AAV vector was successful. Additional analysis showed that murine levels of a-syn in the striatum were not affected. However, further quantitative rater-independent immunofluorescence analyses demonstrated significantly elevated levels of α-syn phosphorylated at serine 129 in the SN. Also, a significant loss of TH-positive soma and fibers in the SN and CPu, respectively were detected, indicating a loss of dopaminergic neurons. Signal of dopamine transporter (DAT) was significantly lower in the AAV-hA53T ipsilateral compared to the contralateral SN. Evaluating inflammatory processes showed that not only microgliosis was evident after AAV-hA53T injection but also CD3-positive T-cells and more specifically cytotoxic CD8-positive T-cells infiltrated the brain.
In summary, the AAV-human A53T α-syn mouse model recapitulates several core features of PD and enables studying A53T α-syn-related pathologies and downstream signaling. The model might be further valuable for the analysis of molecular mechanisms underlying synucleinopathies and pave the way for the development of novel therapeutic interventions.

Disclosures: E. Auer: A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **T. Löffler:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **M. Daurer:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **J. Neddens:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **M. Prokesch:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.09/C2

Topic: C.03. Parkinson's Disease

Support: American Parkinson's Disease Association

Title: The Interaction Between SARS-CoV-2 Infection and Alpha-Synuclein Aggregation in a K18-hACE2 Model of COVID-19

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Abstract: Parkinson's Disease (PD) is a neurodegenerative disease caused by the degradation of dopaminergic neurons located within the substantia nigra pars compacta (SNpc). PD is characterized by four major physical hallmarks: 1) tremors in the hands, legs, or jaw, 2) muscle rigidity, 3) bradykinesia, and 4) impaired balance & coordination. Prior to hallmark onset, which are established diagnostic criteria, neurological symptoms such as depression/anxiety, fatigue, and low motivation are typically present. Our previous work established that COVID-19, caused by severe acute respiratory coronovirus-2 (SARS-CoV-2), can damage dopamine neurons, making them more susceptible to a dopamine neuron toxin, thus presenting a potential risk factor for PD. Interestingly, hyposmia is an early onset symptom of PD and also experienced by roughly 60% of patients who've contracted COVID-19. Furthermore, in vitro evidence has found that SARS-CoV-2 can enhance the accumulation of alpha - synuclein (α-Syn). Since accumulation of α-Syn in Lewy bodies is a definitive feature of PD, SARS-CoV-2 enhancing aggregation of α-Syn could contribute the progression of PD. To test the hypothesis that SARS-CoV-2 enhances α-Syn aggregation in vivo, we injected α-Syn preformed fibril into the striatum then, seven days later, infected K18 human angiotensin converting enzyme transgenic mice (K18-hACE2) with SARS-CoV-2. Thirty days after infection, mice were tested in the open field, Y maze, and rotarod. In the open field, α-Syn+SARS-CoV-2 mice showed significant bradykinesia compared to other groups. No significant differences in the Y maze or rotarod were observed. Currently, α-Syn aggregation in the striatum is being investigated. These preliminary data suggest that SARS-CoV-2 infection can exacerbate the effects of α-Syn preformed fibrils.

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Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.10/C3

Topic: C.03. Parkinson's Disease

Title: Exploring phenotypic variations in Parkinson's disease mutant lines: perspectives from an in vitro alpha-synuclein model and mitochondrial health analysis

Authors: *E. VOLFINZON[1], T.-Y. HO[2], C. BURKE[3], M. TOH[3], S. GYONEVA[2], D. J. STONE[4];
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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder that is caused by a gradual loss of dopamine-producing neurons in the Substantia Nigra Pars Compacta and is accompanied by aggregation of alpha synuclein throughout the brain. This loss of dopamine levels causes motor symptoms such as shaking, rigidity, slowness, and difficulty walking. Though there are medication options that treat the symptoms associated with PD, there are no known drug treatments to slow or stop PD progression, and the root cause of the disease remains unknown. One model to study the potential neuropathological mechanisms underlying PD is through iPSC-derived human disease models, particularly with patient cell lines containing genetic PD variants. The present study aims to model the disease phenotypes *in vitro* using PD patient iPSC-derived neurons carrying a GBA1-N370S and/or SNCA-A53T mutation. We first treated GBA1-N370S neurons with alpha-synuclein pre-formed fibrils (PFFs) to trigger alpha-synuclein aggregation to mimic this major feature of PD pathology in vitro. We observed an increase in alpha-synuclein aggregation in patient iPSC-derived glutamatergic neurons with the GBA1-N370S mutation compared to their isogenic controls. Additionally, it has been reported that there is a deficit in mitochondrial health in PD patients. Here, we used the Seahorse XPro96 Analyzer to explore mitochondrial health in PD patient neurons, measuring both oxygen consumption rate and extracellular acidification rate in live cells. We observed a decrease in mitochondrial ATP production in mutant neurons compared to their isogenic controls. Our *in vitro* alpha-synuclein model of PD, together with the exploration of mitochondrial health, provides a promising strategy for studying the phenotypic differences between the PD mutant lines and isogenic lines. Additionally, this cell model can be instrumental in drug screening, potentially contributing to the development of novel therapeutic PD treatments.

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Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.11/C4

Topic: C.03. Parkinson’s Disease

Support: ASAP

Title: Increased senescence is associated with α-synucleinopathy in the TgA53T mouse model and senolytic treatment delays disease onset

Authors: *I. PODDAR[1,2], R. TAPPE[3], Y. MA[4], Y. ZHANG[5], J. MEINTS[6], N. COURTEMANCHE[3], V. MENON[7], P. ROBBINS[8], L. NIEDERNHOFER[9], D. J. MOORE[10], M. K. LEE[11];
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Abstract: Emerging evidence indicates that cellular senescence is a pathological factor in aging and neurodegenerative diseases, including Parkinson's Disease (PD). Because α-synuclein (αS)-linked pathology and neurodegeneration is mechanistically linked to the pathogenesis of PD, we examined the pathological relationship between α-synucleinopathy and cellular senescence. To study the in vivo relevance, we used a transgenic mouse model of α-synucleinopathy (TgA53T), where rapid and reliable onset of disease was induced by inoculation with human αS PFF. Analysis of TgA53T mice shows that α-synucleinopathy is associated with increased levels of senescence markers including signs of DNA damage response (DDR; γH2Ax, HMGB1), $p16^{INK4a}$, $p21^{Cip1}$ and SASP factors. The nanostring-nCounter transcriptomic analysis also show increase in senescence markers. Cellular localization of senescence markers via immunohistochemistry and RNAscope analysis show that multiple cell types exhibit increased p16 and/or p21, but neurons with αS aggregates are first to show increased senescence markers. To determine the pathologic significance of senescence, the mice were treated with senolytic cocktail [Dasatinib (12 mg/kg) and Quercetin (50 mg/kg) (D+Q)]. Behavior analysis shows that D+Q treatment attenuated preclinical motor and cognitive dysfunction in TgA53T mice. More importantly, D+Q treatment significantly delayed the onset of α-synucleinopathy and reduced neuropathology, including αS pathology, neuroinflammation, and neurodegeneration. D+Q treatment also reduces senescence markers in TgA53T mice. Finally, TgA53T/$Ercc1^{-/\Delta}$ mice develop αS pathology sooner following αS PFF inoculation compared to TgA53T/$Ercc1^{+/\Delta}$ mice, showing that increased senescence accelerates αS pathology. Our data show that cellular senescence is induced by α-synucleinopathy first in neurons and secondarily in glial cells. Further, targeting senescent cells using senolytics may provide neuroprotection from α-synucleinopathy.

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Poster

PSTR329: Alpha-Synuclein: Models

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Program #/Poster #: PSTR329.12/C5

Topic: C.03. Parkinson's Disease

Support: 2023 ASBMB Undergraduate Research Award
2023-2024 Nu Rho Psi Undergraduate Research Grant

Title: Synucleinopathies: Molecular Determinants of β-Synuclein and γ-Synuclein Toxicity in a Yeast Model

Authors: *H. KIERNAN, F. BERTOLOTTI, S. CHANDAVIMOL, T. NASSUNA, R. OSSELBORN, S. GACEK, S. K. DEBBURMAN;
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Abstract: Synucleinopathies, a group of disorders characterized by the abnormal folding and aggregation of proteins from the synuclein family (including α-, β-, and γ-synuclein), encompass Parkinson's Disease (PD), the second most prevalent neurodegenerative condition. While α-synuclein's role in PD is well-researched, less is understood about the involvement of β- and γ-synucleins in neurodegeneration and toxicity. However, two mutations in β-synuclein (P123H and V70M) are associated with Dementia with Lewy Bodies (DLB), and γ-synuclein inclusions are linked with ALS pathology. At SfN2023, we reported that α- and β-synuclein are differentially toxic, whereas γ;;-synuclein is non-toxic in our *Saccharomyces cerevisiae* (budding yeast) PD model system. Here, we further evaluated the toxicity potential of β- and γ-synuclein by looking at their toxicity, localization, and expression using yeast assays. We evaluated substitution mutants for disease-causing β-synuclein mutations V70M and P123H, by changing the original amino acid with a different hydrophobic residue (V70), and with other polar and basic residues (P123). We expressed mutants swapping known familial mutations in α- and β-synuclein onto each other (α-, β- and γ-synuclein). We report that: 1) Substitution mutants show evidence for the gain of polar and basic amino acid cause toxicity in P123H-β-synuclein mutant, while hydrophobicity is key for V70M-β-synuclein toxicity; 2) α-synuclein familial mutations when swapped into β-synuclein show that amino acids A18, A29, A30, E46, G51, and A53 can regulate β-synuclein toxicity; 3) however, γ-synuclein's non-toxicity is unaltered when swapped with α-/β-, familial mutations at A18, A30, E46, and V70. This study highlights the usefulness of yeast models in better understanding β- and γ-synuclein pathogenicity in neurodegeneration.

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Poster

PSTR329: Alpha-Synuclein: Models

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.13/C6

Topic: C.03. Parkinson's Disease

Support: ASAP

Title: In vitro seeding capacity of alpha-synuclein preformed fibrils predictive of PD-like pathology in in vivo mouse models

Authors: *L. E. HAMPTON[1], P. RIVA[1], Y. CHEN[1], J. M. WEBSTER[2], A. S. HARMS[2], W. D. HIRST[3], J. H. KORDOWER[4], K. E. GLAJCH[1];
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Abstract: Parkinson's disease (PD) research has been constrained by a paucity of animal models that capture a key feature of PD pathology, toxic α-synuclein protein aggregates. The preformed fibril (PFF) mouse model of PD is a promising development in the search for such a mouse model; however, lot-to-lot variability in PFF seeding capacity has highlighted the need to assess *in vitro* QC best practices and understand how these data might better predict *in vivo* results. Building on current literature, we characterized commercially available and internally produced PFFs using both *in vitro* and *in vivo* model systems. Primary rodent cortical neurons were treated with PFFs, vehicle, or monomeric alpha-synuclein for fourteen days and then evaluated for phosphoserine-129 (pS129) positive aggregates by immunofluorescence; in parallel, wild-type C57BL6 mice were unilaterally injected with the same treatment groups and sacrificed at 1-month, 3-months, and six-months post-injection. Both monomeric and fibrillar alpha-synuclein were evaluated by size (DLS), structure (TEM), aggregation propensity (ThT and sedimentation), and cell toxicity. Despite lot-to-lot consistency in DLS, TEM, and ThT parameters, primary neuronal cultures treated with PFFs revealed substantial intra-lot variability in pS129 pathology; these results were reproduced in multiple independent experiments. While similar intra-lot variability in PFF induced-pS129 aSyn pathology was observed *in vivo*, we found a positive correlation between the degree of pS129 pathology in vitro and in vivo for a given lot. Furthermore, pS129 pathology *in vitro* was also predictive of *in vivo* nigrostriatal degeneration in both severity and onset. These results emphasize the importance of *in vitro* quality control assays for reproducibility and efficacy of the PFF mouse model.

Disclosures: L.E. Hampton: A. Employment/Salary (full or part-time):; Biogen. **P. Riva:** A. Employment/Salary (full or part-time):; Biogen. **Y. Chen:** A. Employment/Salary (full or part-time):; Biogen. **J.M. Webster:** None. **A.S. Harms:** None. **W.D. Hirst:** None. **J.H. Kordower:** None. **K.E. Glajch:** A. Employment/Salary (full or part-time):; Biogen.

Poster

PSTR329: Alpha-Synuclein: Models

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Program #/Poster #: PSTR329.14/C7

Topic: C.03. Parkinson's Disease

Support: ASAP-020566
Tan Foundation
Broetje Foundation
Larry L Hillblom Foundation

Title: Lrrk2-mediated endolysosomal dysregulation in pff-induced neuronal senescence

Authors: X. ZUO[1], A. JOHNSTONE[2], X.-Q. CHEN[4], U. DAS[3], *W. C. MOBLEY[5]; [1]Neurosciences, UCSD, SAN DIEGO, CA; [2]Neurosciences, UCSD, San Diego, CA; [3]Dept. of Neurosciences, UCSD, UCSD, La Jolla, CA; [4]Neurosciences, UCSD/Neuroscience, La Jolla, CA; [5]Neurosciences, Univ. of California San Diego Dept. of Neurosciences, La Jolla, CA

Abstract: In this study, we employed a PFF in vitro model to elucidate mechanisms of pathogenesis in cortical neurons. Treatment with preformed fibrils (PFF) led to significant enlargement of lysosomes and increased levels of lysosomal proteins, as confirmed by mass spectrometry of isolated organelles. This increase coincided with a marked reduction in lysosomal proteolytic capacity and leakage of lysosomal enzymes into the cytosol. We also observed a deterioration in nuclear architecture, indicated by decreased laminB1 levels, collectively suggesting a senescence phenotype in neurons. Transcriptomic analysis further revealed an upregulation of genes associated with cellular senescence pathways following PFF exposure. Additionally, we explored the effects on upstream endosomal compartments and observed significant hyperactivation of Rab5, characterized by enlarged Rab5-positive endosomes and increased levels of GTP-bound Rab5 protein. Importantly, LRRK2 was recruited to these endosomes and was identified as the kinase responsible for Rab5 phosphorylation in PFF-treated neurons. Intervention with the specific LRRK2 kinase inhibitor, MLi-2, effectively reversed the increase in lysosomal enzyme levels and restored chromatin structure, as demonstrated by ATAC-seq analysis. Our findings underscore a critical role for LRRK2 in PFF-induced endolysosomal dysregulation and neuronal senescence, enhancing our understanding of the molecular pathways and offering new therapeutic avenues targeting LRRK2 and Rab5 activities.

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Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.15/C8

Topic: C.03. Parkinson’s Disease

Support: MJFF 02031

Title: Impact of a-Synuclein pathology on corticostriatal synapses in Parkinson's disease

Authors: *H. CHALLA[1], C. BRZOZOWSKI[1], L. A. VOLPICELLI-DALEY[2];
[1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]UAB, Birmingham, AL

Abstract: Parkinson's disease (PD) is the most common neurodegenerative motor disorder, pathologically characterized by proteinaceous α-synuclein aggregation, termed Lewy Pathology. In human post-mortem PD brain and rodent α-synuclein aggregation models, Lewy Pathology is shown to accumulate in cortical layer V neurons that project to the striatum. Layer V projection neurons in the pre-supplementary motor area (pre-SMA), homologous to the secondary motor cortex (M2) in mice, have been shown distinct vulnerability in the PD post-mortem brain. M2 corticostriatal projections are associated with executive function and movement planning, which are often disrupted in PD. However, little is known about how Lewy pathology affects the overall functionality of these synapses on striatal spiny projection neurons. Our research aims to induce α-synuclein pathology in the M2 cortex to decipher the impact of aggregated α-synuclein on the morphology of M2-corticostriatal synapses. To recapitulate α-synuclein aggregation in rodent models, we utilize the preformed fibril (PFF) model for template corruption of endogenously expressed α-synuclein. PFF or control α-synuclein monomer was injected into the M2 cortex to study M2-specific inputs in the striatum. To study corticostriatal synapses, we combined immunofluorescence techniques with IMARIS software to quantify synaptic densities and visualize the impact of pathological α-synuclein on presynaptic terminals. Additionally, striatal and cortical protein lysates of animals receiving either PFF or control injections will be assessed for protein expression of synaptic markers. For 6 weeks post M2 cortical PFF injections, we observed robust somal and neuritic pathology in layer V neurons of the M2 cortex, neighboring cortical areas, and areas projecting to M2, including the amygdala and orbital area. We also observed neuritic pathology in the striatum, which predominantly overlapped with the cortical, presynaptic terminal marker vGlut1. Using our combined analysis approach, we found a significant reduction in corticostriatal synaptic loci in the dorsal striatum of M2-PFF injected animals. Additional data indicate morphological changes to the volumes of cortical presynaptic terminals upon aggregate formation. Our results point to an important role of cortical Lewy Pathology in the functionality of corticostriatal synapses. Future studies will assess the spread and impact of cortical α-synuclein pathology on animal brain areas and behavior.

Disclosures: H. Challa: None. **C. Brzozowski:** None. **L.A. Volpicelli-Daley:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.16/C9

Topic: C.03. Parkinson's Disease

Title: Retina mirrors the neuroinflammatory response in a rat model of Parkinson's disease

Authors: *C. BURGALETTO[1], A. CANTONE[1], G. DI BENEDETTO[1], M. PALMAS[2], G. GAUDIO[1], C. BELLANCA[1], A. R. CARTA[2], R. BERNARDINI[1], G. CANTARELLA[1];

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Abstract: Parkinson's disease (PD) is a debilitating neurodegenerative synucleinopathy characterized by pathological deposition of alpha-synuclein (αSyn), primarily affecting neurons of the motor system. Despite its motor-centric characterization, visual dysfunction and retinal ultrastructure and function impairment represent well-documented non-motor changes of PD. Given the central role of αSyn in PD brain, we assessed whether the retina, as an extension of the central nervous system (CNS), is affected in a rat model of PD neuropathology based on the intranigral bilateral infusion of toxic preformed oligomers of human α-synuclein (H-αSynOs). Retinal tissue parameters, such as the expression pattern of a focused set of miRNAs, as well as of inflammatory mediators, were assessed after injection. Rats receiving intracerebral injection of H-αSynOs exhibited high levels of retinal α-synuclein and phospho-α-synuclein, along with decreased dopaminergic neuron count, marked by reduced tyrosine hydroxylase (TH) expression. Bioinformatic analysis of PD-associated miRNAs, also revealed heightened expression of miR-384-5p, which inversely correlated with the expression of its predicted molecular target, SIRT1, in rats receiving H-αSynOs infusion. Furthermore, a widespread activation of both GFAP and Iba-1, indicating heightened proinflammatory cytokine signaling downstream of TLR4, was detected in the retina of rats receiving the H-αSynOs infusion. These data suggest that molecular alterations observed in the retina closely mirror the underlying pathological mechanisms occurring in PD. This provides valuable insights for proactive interventions aimed at addressing PD-related pathology.

Disclosures: C. Burgaletto: None. **A. Cantone:** None. **G. Di Benedetto:** None. **M. Palmas:** None. **G. Gaudio:** None. **C. Bellanca:** None. **A.R. Carta:** None. **R. Bernardini:** None. **G. Cantarella:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.17/C10

Topic: C.03. Parkinson’s Disease

Title: An in vitro alphasynuclein hyperexpression model for Parkinsons disease

Authors: O. H. SCHROEDER, *L. SCHULTZ, A.-M. KNOSPE, M. WINKLER, K. JÜGELT; NeuroProof Systems GmbH, Rostock, Germany

Abstract: Parkinson's Disease (PD) is the second most common neurodegenerative disease in the elderly population, with a higher prevalence in men, independent of race and social class; it affects approximately 1.5 to 2.0% of the elderly population over 60 years and 4% for those over 80 years of age. There is no cure for PD and the etiology of PD is not fully understood.
Most forms of PD are sporadic with a genetic predisposition and environmental toxin influence.

Alpha-synuclein (SNCA) is a main player in Parkinson's disease, inhibition of it is one therapeutic approach for Parkinson's disease.
In this study we have investigated the effect of SNCA overexpression in electrophysiological activity patterns.
We used an AAV SNCA overexpression construct to transduce alpha-synuclein overexpression in midbrain cultures from mice.
Transduction with AAV SNCA overexpression constructs were optimized and validated with GFP constructs of midbrain cultures of mice on MEA recording plates.
Alpha-synuclein overexpressing cultures showed less activity measured in spike and burst rate, but an increased synchronization.
We demonstrated that alpha-synuclein overexpression in midbrain cultures of mice on MEA well plates can be a new functional phenotypic screening approach for PD.

Disclosures: O.H. Schroeder: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroProof Systems GmbH. **L. Schultz:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH. **A. Knospe:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH. **M. Winkler:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH. **K. Jügelt:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.18/C11

Topic: C.03. Parkinson's Disease

Support: Fonds de Dotation Clinatec
Fondation de l'avenir
Enhanced Eurotalents Program

Title: Establish and characterize chronic animal model representative of Parkinson's disease physiopathology

Authors: M. VIONNET[1], I. HORVATH[2], R. KUMAR[2], P. WITTUNG STAFSHEDE[2], N. TORRES[1], A.-L. BENABID[1], ***J. MOLET**[1];
[1]CEA DTIS SRBN, Grenoble, France; [2]Life Sci. Dept., Chalmers Univ. of Technol., Gothenburg, Sweden

Abstract: Rationale: Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, resulting from progressive death of dopaminergic neurons in the Substantia Nigra and leading to motor disability. The typical motor symptoms are a combination of bradykinesia, resting tremor and rigidity. Notably, methods to diagnose PD are currently dependent on the presence of these motor signs and a good response to dopaminergic therapy

during DOPA challenge (L-DOPA or levodopa, the most effective replacement agent for the treatment of motor symptoms in PD). Actually, there is no cure for this disease and its pathogenesis is still unclear. Unfortunately, most animal models do not reproduce the progressive nature of PD as well as its major hallmarks. Thus, the development of a chronic animal model of PD which ensures progressive and stable neurodegenerative level associated with motor deficits is crucial, notably to understand PD pathogenesis and evaluate new therapy. In this study, we characterize a chronic animal model that mimic PD physiopathology, based on alpha-synuclein (α-syn) intranasal administration. **Methods:** At 8 weeks, male BALB/cByJ mice were subjected to daily intranasal bilateral administration of 15 µg of α-syn fibrils or vehicle (Veh) over 14 days. To evaluate the effects of transmissible α-syn pathology on motor and emotional behaviors, mice were exposed to open field and rotarod tests before α-syn administration (basal level) and at 90 and 180 days post injection (dpi). At 180 dpi, animals were treated with L-DOPA to investigate whether this dopaminergic therapy could reverse the motor coordination deficits. Dopaminergic neurodegeneration was evaluated using tyrosine hydroxylase (TH) immunohistochemistry (IHC). **Results:** In this study, we showed that intranasal administration of α-syn fibrils to mice resulted in a progressive and chronic parkinsonian phenotype associated with locomotor and nigrostriatal impairments in dopamine integrity. We found that L-DOPA injection, in α-syn mice, rescued locomotor deficits. **Conclusions:** Our study reveals an original α-syn model of PD that progresses, allowing motor symptoms and dopaminergic neurodegeneration with time.

Disclosures: M. Vionnet: None. **I. Horvath:** None. **R. Kumar:** None. **P. Wittung Stafshede:** None. **N. Torres:** None. **A. Benabid:** None. **J. Molet:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.19/C12

Topic: C.03. Parkinson’s Disease

Title: Evaluation of novel patient-derived alpha-synuclein fibril strains in seeded-aggregation models of Parkinson’s disease

Authors: *N. PATEL[1], A. SOKRATIAN[1], S. STRADER[1], A. B. WEST[2];
[1]Duke Univ., Durham, NC; [2]Pharmacol., Duke Univ., Durham, NC

Abstract: Accumulation of alpha-synuclein fibrils into larger aggregates is a central hallmark of pathologies associated with Dementia with Lewy Bodies (DLB), Parkinson’s disease (PD), Multiple System Atrophy (MSA). Recent efforts towards uncovering structural compositions of alpha-synuclein fibrils from postmortem brain samples revealed a presence of multiple conformations of fibrils that can be distinct in these subtypes of synucleinopathies. A prevalant hypothesis suggests that the structural composition encoded in fibril variants holds a crucial functional component that may contribute to disease manifestation and severity. To test this

hypothesis, we used amplification assays to generate two distinct patient-derived populations of homogenous alpha-synuclein fibrils with distinct structural characteristics and applied them in a series of informative models. Focusing on two DLB cases selected based on unique amyloid dye profiles and amplification kinetics in real-time quaking induced aggregation reactions, structures of the fibrils were resolved at the atomic level using CryoEM. To investigate propagation properties associated with these fibril strains in models, we implemented the PFF model using human-PAC-WT-*SNCA*+/+/*Snca*-/- transgenic mice, which overexpress wild-type human alpha-synuclein without mouse alpha-synuclein interference. Three months after unilateral injections with PFFs in the motor cortex, we discovered significantly different levels of pS129-alpha-synuclein pathology between the strains, suggesting that strain structure may influence critical downstream endpoints. We will continue to resolve structure to function relationships that drive these differences observed in the models. This study supports the hypothesis that alpha-synuclein strain substructures may convey specific functional characteristics to disease endpoints and associated pathological features.

Disclosures: N. Patel: None. **A. Sokratian:** None. **S. Strader:** None. **A.B. West:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.20/C13

Topic: C.03. Parkinson’s Disease

Title: Further characterisation of the AAV A53T alpha-synuclein mouse model of Parkinson's disease.

Authors: D. AREF, T. H. JOHNSTON, P. HOWSON, *M. HILL;
Atuka Inc., Toronto, ON, Canada

Abstract: Parkinson’s disease (PD) is a progressive disorder affecting 1-2% of the global population over the age of 65. One of the hallmarks of PD is the widespread presence of pathological forms of α-synuclein (aSyn), a presynaptic neuronal protein, which leads to degeneration and death of dopaminergic neurons in the Substantia Nigra pars compacta (SNpc). Developing and refining animal models that replicate the clinical progression of the disease is invaluable in aiding our understanding of PD and the testing of potential therapeutics. The viral vector mediated overexpression of pathological forms of aSyn of mice is one such model. Adenovirus (AAV1/2) mediated overexpression of pathological human aSyn (hA53T-aSyn), injected into the SN of mice using stereotaxic techniques is an established model of PD. In its current form, it has been shown to produce significant motor impairment at 5-weeks and 9-weeks post viral vector injection and degeneration of the nigrostriatal tract at 10-weeks post viral vector administration (Ip et al. 2017). In this study, we aimed to evaluate the level of neurodegeneration within a shorter time frame. We assessed motor impairment at 3-weeks and 6-weeks post injection in male, C57Bl/6j mice (8 weeks of age at time of surgery). In addition the level of

nigrostriatal degeneration was evaluated at 6-weeks post injection on several endpoints, including quantification of striatal Dopamine Transporter (DAT) levels by autoradiography, quantification of striatal dopamine and metabolites via Liquid Chromotography and Mass Spectrometry (LC-MS/MS), quantification of nigral dopaminergic neurons via stereology, and assessment of level of neuroinflammation via immunohistochemistry. In this study, we showed significant degeneration within the nigrostriatal tract at 6-weeks post pathological aSyn overexpression on a variety of measured endpoints. Therefore, the time frame of this model can be shortened by 4 weeks without compromising the observed level of neurodegeneration within the nigrostriatal tract.

Disclosures: D. Aref: A. Employment/Salary (full or part-time):; Atuka Inc. **T.H. Johnston:** A. Employment/Salary (full or part-time):; Atuka Inc. **P. Howson:** A. Employment/Salary (full or part-time):; Atuka Inc. **M. Hill:** A. Employment/Salary (full or part-time):; Atuka Inc..

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.21/C14

Topic: C.03. Parkinson's Disease

Support: NSF 2023004
Paul H Boerger Fund of Delaware Community Foundation
INBRE P20GM103446

Title: Phosphorylation and aggregation of alpha-synuclein in a cell culture model of synucleinopathy

Authors: *M. ABEER[1], T. PETERSEN[1], M. DOPLER[2], M. A. GITCHO[3];
[1]Delaware State Univ., Dover, DE; [2]Biol., Delaware State Univ., Dover, DE; [3]Biol. Sci., Delaware State Univ., Ocean City, MD

Abstract: Alpha-synuclein (SNCA) is a major pathological protein involved in Parkinson's disease (PD) which is a neurodegenerative disorder that affects predominantly the dopaminergic neurons in the substantia nigra of the brain. Some common symptoms of PD include tremors, bradykinesia, hypokinesia and limb stiffness or rigidity. In addition to these motor symptoms, there are some non-motor symptoms as well including sleep disorder, anxiety and a variety of cognitive impairments. Unfortunately, the cause of this disease remains unknown. However, accumulation of abnormal SNCA known as Lewy bodies in the substantia nigra is common in PD patients. SNCA is a neuronal protein that helps regulate synaptic vesicle supply, neurotransmitter (dopamine) release, membrane structure and other presynaptic functions. These missense mutations include A53T, A30P, E46K, E83Q, H50Q and G51D. Mutations in the SNCA gene are a rare cause of autosomal dominant familial PD. How these mutations initiate the disease cascade remains largely unknown. We are currently characterizing human embryonic

kidney cells (HEK 293T), rat dopaminergic cells (N27), neuroblastoma cells (SH-SY5Y) and mouse primary cortical neurons to overexpress various combinations of SNCA familial mutations (E46K, A53T and E83Q). Preliminary results show that when A53T/E46K and/or A53T/E46K/E83Q are overexpressed, there is an increase in SNCA phosphorylation and aggregation. Currently, we are experimenting with Lenti-viral transduction to produce SNCA overexpression in the HEK 293T cells. Bioenergetic experiments will be carried out to evaluate the mitochondrial morphology of the cells upon the overexpression of mutated SNCA. The overall goal of this study is to identify the most effective combination of mutants that replicate some aspects of human pathology. We hope this *in vitro* model will provide insight into the pathogenesis of this devastating disease.

Disclosures: M. Abeer: None. **T. Petersen:** None. **M. Dopler:** None. **M.A. Gitcho:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.22/C15

Topic: C.03. Parkinson's Disease

Title: Characterization of pSer129-αSyn pathology and NFL release across in vivo, ex vivo, and in vitro models of PFF-induced αSyn aggregation

Authors: *M. HANSEN[1], F. SOTTY[2], M. AMBJORN[1];
[1]Functional and Cell. Pharmacol., H Lundbeck A/S, Valby, Denmark; [2]Neuroscience, Histology and Pathology Models, H. Lundbeck A/S, Valby, Denmark

Abstract: Protein aggregation is a predominant feature of many neurodegenerative diseases, including synucleinopathies, which are characterized by cellular inclusions containing α-Synuclein (αSyn) phosphorylated at serine 129 (pSer129). In the present study, we characterized the development of αSyn pre-formed fibril (PFF)-induced pSer129-αSyn pathology in F28tg mice overexpressing human wild-type αSyn, as well as in ex vivo organotypic cultures and in vitro primary cultures from the same mouse model. Concurrently, we collected cerebrospinal fluid (CSF) from mice and conditioned media from ex vivo and in vitro cultures and quantified the levels of neurofilament light chain (NFL), a biomarker of neurodegeneration. We found that the intra-striatal injection of PFFs induces the progressive spread of pSer129-αSyn pathology and microglial activation in vivo, as well as modest increases in NFL levels in the CSF. Similarly, PFF-induced αSyn pathology occurs progressively in ex vivo organotypic slice cultures and is accompanied by significant increases in NFL release into the media. Using in vitro primary hippocampal cultures, we further confirmed that pSer129-αSyn pathology and NFL release occur in a manner that correlates with the fibril dose and the level of the αSyn protein. Overall, we demonstrate that αSyn pathology is associated with NFL release across preclinical models of seeded αSyn aggregation and that the pharmacological inhibition of αSyn aggregation in vitro also significantly reduces NFL release.

Disclosures: M. Hansen: A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **F. Sotty:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **M. Ambjorn:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.23/C16

Topic: C.03. Parkinson's Disease

Support: NIH Grant T32GM144856
NIH Grant 5R35ES035043-02

Title: Pathogenic Alpha-Synuclein Induces cGAS-STING Activation and DNA Damage in Astrocytes.

Authors: *O. A. YANOURI, A. J. SCHULLER, S. M. ROCHA, R. B. TJALKENS; Envrn. and Radiologic Hlth. Sci., Colorado State Univ., Fort Collins, CO

Abstract: Parkinson's disease (PD) is the second most prevalent neurodegenerative disease and is associated with chronic neuroinflammation mediated by reactive, pro-inflammatory glial cells that contributes to disease progression. Acute encephalitis in response to viral infection has been demonstrated to increase the risk of developing post-encephalitic parkinsonism, implicating antiviral signaling in aberrant neuroinflammation and PD pathophysiology. Prior work by our group demonstrates the pivotal role astrocytes play in the initiation and maintenance of parenchymal immune modulation and PD pathogenesis. A pathway of interest is cGAS-STING, an innate cytosolic nucleotide sensing system that mediates innate type-I anti-viral interferon responses. Recent studies demonstrate attenuation of this pathway is sufficient to protect against dopaminergic neurodegeneration and motor dysfunction in the preformed fibril (PFF) model of PD. We postulated that toxic alpha-synuclein (α-Syn) species trigger cGAS-STING mediated inflammation in astrocytes through induction of DNA damage and cytosolic release. To test this hypothesis, primary mixed glial cultures containing astrocytes and microglia were isolated from prenatal (P1) C57bl/6 mice and treated with oligomeric and fibrillar α-Syn species. Astrocytic cGAS-STING activation and DNA damage were examined by immunofluorescence microscopy for the activated phosphorylated form of STING (pSTING) and γH2A.x, respectively, in $GFAP^+$ astrocytes. We observed that treatment with fibrillar α-Syn at 1 and 6 μg/mL for 24 hours induced robust IFN-β release and pSTING and γH2A.x signaling, respectively. Moreover, co-treatment with the STING antagonist H-151 significantly attenuated γH2A.x fluorescence and INF-β secretion. These findings suggest pathological α-Syn species are capable of activating the cGAS-STING pathway, and the combined effects of toxic fibrils and STING signaling further contribute to DNA damage. Future studies will investigate the extent of mitochondrial and nuclear DNA release in response to pathologic synuclein species in the context neuroinflammatory activation of astrocytes.

Disclosures: O.A. Yanouri: None. **A.J. Schuller:** None. **S.M. Rocha:** None. **R.B. Tjalkens:** None.

Poster

PSTR329: Alpha-Synuclein: Models

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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Topic: C.03. Parkinson's Disease

Support: The William N and Bernice E Bumpus Foundation Postdoctoral Fellowship Award for M.J.J.
Barnard College SRI Fellowship For O.S.
NIH Grant 1R21AG085144

Title: Dissection of differential susceptibility of dopaminergic neurons to human wild-type and p.A53T α-synuclein cell-specific overexpression driven by systemically-delivered AAV.

Authors: *M. J. JENNINGS[1], O. STANGE[2], A. CHAVEZ[3], S. E. PRZEDBORSKI[1];
[1]Columbia Univ., New York, NY; [2]Barnard College, Columbia Univ., New York, NY; [3]UCSD, La Jolla, CA

Abstract: Pathologically, the protein α-synuclein forms protofibrils and eventually larger inclusions, termed Lewy neurites and Lewy bodies. Both overexpression and point mutations affecting the biophysical properties of α-synuclein have been shown to cause genetic forms of Parkinson's disease, while sporadic cases of Parkinson's disease and dementia with Lewy bodies are also associated with aberrant α-synuclein accumulation. Previously generated α-synuclein overexpression mouse models are hindered by either only mild induction of expression or by the use of invasive stereotaxic injections.
Using AAV-PHP.eB we induced overexpression of either human wild-type ($hSNCA^{WT}$) or Parkinson's-associated p.A53T variant α-synuclein ($hSNCA^{A53T}$) specifically in CNS dopaminergic neurons of mice. This demonstrated robust accumulation of phosphorylated α-synuclein (p-α-synuclein) in TH+ neurons apparent by 3-weeks post-injection and increasing in number through to 8-weeks post-injection. By profiling TH and p-α-synuclein immunoreactivity across the entire ventral midbrain, and then employing an automated cell intensity profiling pipeline, we showed that while absolute numbers of p-α-synuclein+ neurons were stable between 8-weeks and 28-weeks post-injection, per-cell intensity of both p-α-synuclein and TH immunoreactivity decreased with further time.
We then used this system to determine the effect of a recently identified modifier of cellular processing of α-synuclein by combining AAV-induced α-synuclein overexpression with a gene silencing strategy to determine both the base pathological effect of gene silencing in parallel with the effect of gene silencing under conditions of synucleinopathy stress.

Disclosures: M.J. Jennings: None. **O. Stange:** None. **A. Chavez:** None. **S.E. Przedborski:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.25/C18

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation

Title: Effects of alpha-synuclein pS129 on the phosphorylation of neighboring residues Y125 and Y136

Authors: *W. QI[1,2], J. HENSEL[3], J.-C. ROCHET[1,2];
[1]Borch Dept. of Medicinal Chem. & Mol. Pharmacol., Purdue Univ., West Lafayette, IN; [2]Purdue Institute for Integrative Neuroscience, West Lafayette, IN; [3]Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Parkinson's disease (PD) is a neurologic disorder defined pathologically by the degeneration of dopaminergic neurons and the accumulation of Lewy bodies, which are enriched with aggregated forms of the presynaptic protein alpha-synuclein (aSyn). Two high priorities in the synucleinopathy field are to understand how different combinations of aSyn post-translational modifications (PTMs) affect the protein's aggregation, and how the binding properties of antibodies specific for modified forms of aSyn are influenced by PTMs located near the target epitope. pS129-aSyn is widely used as a marker for aSyn inclusion formation and has been shown to be increased in both cellular and animal models of PD. pY125-aSyn is reported to be present at a higher level in the brains of synucleinopathy patients, but it has been found in different studies to inhibit aSyn oligomer formation or to have no effect. Therefore, the role of Y125 phosphorylation in modulating aSyn aggregation is unclear. Moreover, little is known about the impact of neighboring pS129 on Y125 phosphorylation. Here, we examined the tyrosine phosphorylation of recombinant human WT aSyn and a semi-synthetic pS129-aSyn variant incubated with increasing amounts of Syk tyrosine kinase. pY125- and pY136-aSyn were detected via Western blotting using antibodies specific for each phosphorylation site. The yield of pY125-aSyn increased with increasing Syk concentration for both the WT and pS129-aSyn variants, whereas the yield of pY136-aSyn only increased systematically for the WT protein, but not pS129-aSyn. The efficiency of Syk-mediated phosphorylation was identical for Y125 and Y136 in the context of WT aSyn, whereas phosphorylation occurred preferentially at Y136 or equally at both sites when pS129-aSyn was incubated with low or high amounts of kinase, respectively. With a fixed amount of Syk, the presence of pS129 in the semi-synthetic variant was found to increase Syk-mediated phosphorylation of both Y125 and Y136 compared to WT aSyn. From these data, we infer that S129 phosphorylation alters the conformation of the aSyn C-terminal domain, making Y125 and, to an even greater degree, Y136 more accessible for Syk

phosphorylation. Moreover, S129 phosphorylation may favor electrostatic interactions between Syk and aSyn, given the presence of acidic residues in the Syk recognition sequence. These results advance our understanding of the role of PTMs in modulating aSyn conformational properties, potentially impacting the formation of neurotoxic aggregates in the brains of PD patients.

Disclosures: W. Qi: None. **J. Hensel:** None. **J. Rochet:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.26/C19

Topic: C.03. Parkinson's Disease

Title: Enhancing motor, cognitive, and neuroinflammatory aspects in an experimental model of Parkinson's: the beneficial role of physical exercise

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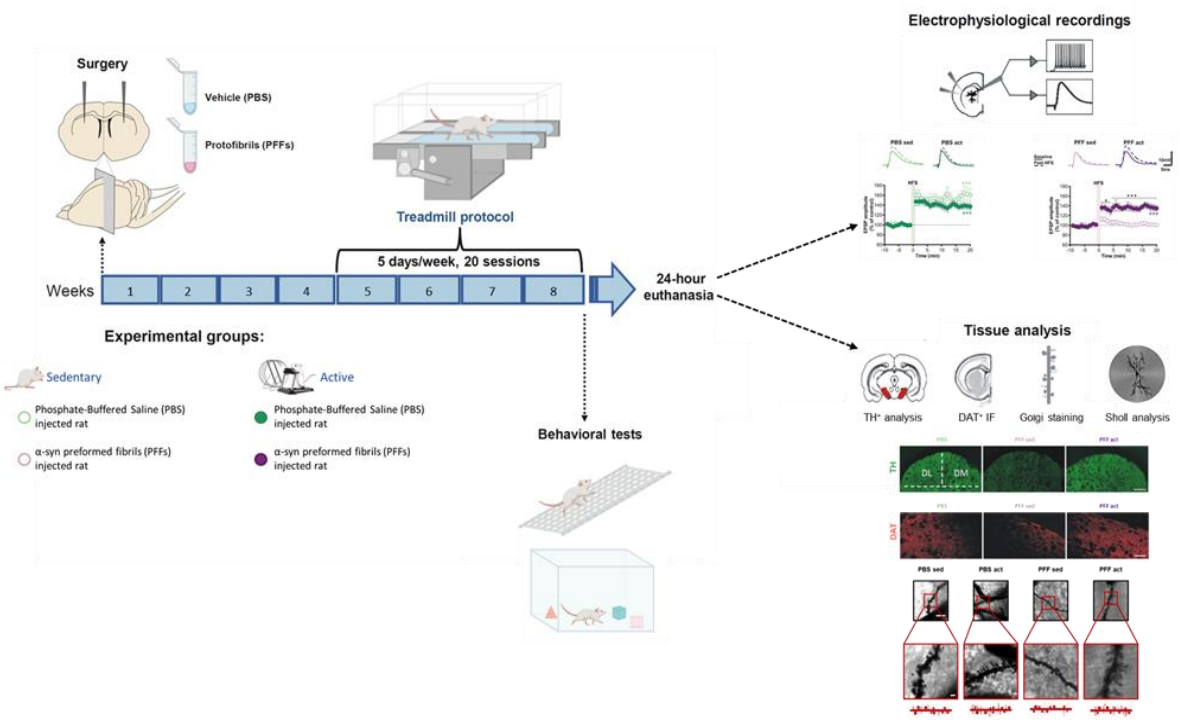
Abstract: Parkinson's disease (PD) is characterized by the formation of Lewy body aggregates and dopaminergicneuronal loss. Clinical studies suggest that motor symptoms associated with PD can be improved throughphysical activity, but the underlying mechanisms are not fully understood. In this study, we investigatedwhether intensive treadmill exercise can counteract nigrostriatal neurodegeneration in rats injected withintrastriatal alpha-synuclein (α-syn) preformed fibrils (PFFs). To assess the effects of treadmill activity, weexamined the survival of striatal dopaminergic neurons and their functional integrity. Additionally, we analyzedthe structural plasticity of postsynaptic compartments, dendritic spine density of striatal spiny projectionneurons, and the effects of exercise on modulating neuroinflammation. Interestingly, in active PFF-treated rats,we observed a higher number of surviving Substantia Nigra pars compacta (SNpc) neurons, coupled withincreased density of dopaminergic terminal fibers, and enhanced spine density in the spiny projection neurons(SPNs), compared to the sedentary PFF group. These structural changes were also associated with improvedfunctional outcomes, as active animals exhibited better motor coordination and memory performance, whichrequire

intact striatal function. Moreover, to assess the potential beneficial role of physical activity, weexamined the involvement of brain-derived neurotrophic factor (BDNF). Corticostriatal Long TermPotentiation in active animals subjected to treadmill exercise was found dependent on BDNF-TrkB pathwayactivation. These findings suggest that BDNF may be implicated in the beneficial effects of treadmill exercise,possibly associated with the expression of LTP in SPNs. In conclusion, our study provides clear evidence thatintensive exercise is effective in counteracting α-syn aggregates spreading, preventing early synaptic deficits,reducing neuroinflammation, and improving functional recovery in this experimental model of PD.



Disclosures: F. Servillo: None. **M. De Carluccio:** None. **G. Marino:** None. **F. Campanelli:** None. **G. Natale:** None. **M. Viscomi:** None. **V. Ghiglieri:** None. **P. Calabresi:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.27/C20

Topic: C.03. Parkinson’s Disease

Support: HU22C0115

Title: Escherichia coli K1 meningitis induces H3K4me3 trimethylation-mediating systemic neurotoxic synucleinopathy in a gut-brain axis microphysiological system

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Abstract: *Escherichia coli* K1 (*E. coli* K1) neonatal meningitis causes life-threatening infections of the meninges and central nervous systems with high morbidity and mortality. However, the mechanism by which *E. coli* K1 may cause long-term neuropathies is poorly understood due to the absence of a suitable model for the systemic study of multi-organ interactions and multiplex effects upon early *E. coli* K1 infection. Here, we provide a platform for investigating how *E. coli* K1 meningitis induces H3K4me3 trimethylation-mediating systemic neurotoxic synucleinopathy, leading to hyper-neuroinflammation via antiviral-like signaling in the gut-brain axis meningitis induction. Firstly, our findings reveal that intestinal and peripheral IL-6 promotes blood-brain barrier injury via the p38/p65 pathway, leading to NLRP3 priming during *E. coli* K1 meningitis. We further explore how reactive astrocytic IFN-γ inhibits microglial phagocytosis exacerbating neurotoxic microgliosis via paired activation of NLRP3 inflammasome and antiviral signaling pathway upon early *E. coli* K1 meningitis, evidenced by the increased expression of inflammatory markers, oxidative stress, and the release of neurotoxic factors. Finally, we discover early *E. coli* K1 meningitis induces permanent cell cycle arrest via activation of p16/p21 in neurons leading to the accumulation of α synuclein via H3K4me3 histone modification, promoting neurotoxic synucleinopathy, ultimately inciting microgliosis. Taking it all together, our findings may contribute to developing novel strategies for post-bacterial meningitis treatment aimed at preventing Parkinson's disease initiation and progression.
Keywords: Escherichia coli K1, organ-on-chip, gut-brain axis, hyper-neuroinflammation, H3K4me3 trimethylation, synucleinopathy, Parkinson's disease**.**

Disclosures: V. Tran: None. **H. Cho:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

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Program #/Poster #: PSTR329.28/C21

Topic: C.03. Parkinson's Disease

Support: Medical Research Center (NRF-2019R1A5A2026045) of National Research Foundation of Korea (NRF) funded by the Korean Government
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Okinawa Institute of Science and Technology Graduate University from the Government of Japan

Title: Human striata-midbrain assembloids: A new modeling system for Parkinson's disease research

Authors: *M.-K. SHIN[1,2], H. TRAN[6], X. YEO[7,8], S. JUNG[9], C. DENMAN[6], M. KIM[1,3], D. JEON[1,3], H. KIM[1,2], J. MUN[10], E. LEE[3,4], S. PARK[5,2,3], B. KUHN[6], G. W. ARBUTHNOTT[6], J. JO[1,6,2,3];
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Abstract: Parkinson's disease (PD) is a neurodegeneration disease with the progressive loss of dopaminergic (DA) neurons and aggregation of alpha-synuclein (α-syn) in the *substantia nigra pars compacta* (SNpc). The α-syn is one of the major components of lewy body and known as the hallmarker of PD. Most PD model systems focus on non-human experiments, limiting their ability to mimic human disease models and find effective drugs. Recent advances in human pluripotent stem cell (hPSC)-derived organoid technology facilitate the study of brain development and neurological disorders. In this study, we developed human striatal-midbrain assembloids (hSMAs) by fusing human midbrain organoids (hMOs) and human striatal organoids (hSOs) generated from hPSCs. These hSMAs replicate basal ganglia circuits, comprising both striatal and midbrain components, facilitating the investigation of reciprocal projections like nigrostriatal and striatonigral pathways crucial for motor function. We conducted immunohistochemistry, western blot analysis, electrophysiological recordings, qRT-PCR, and RNA sequencing to characterize neuronal projection and neural activity. As a results, hSO contained various cell types including oligodendrocytes, astrocytes, and GABAergic neurons. Our new method for hMO generation produced diverse cell types and exhibited a transcriptome profile similar to *in vivo* midbrain. Additionally, hSMAs, particularly those formed from *TH*-EGFP reporter hPSCs, confirmed DA projection through immunohistochemistry analysis and exhibited higher activity compared to hSOs and hMOs. In contrast, hSMAs with *SNCA* overexpression (*SNCA* O/E) manifested shorter and fewer axonal projections, lower network burst frequency, and firing rate compared to wild-type hSMAs. Biochemistry analysis have been elevated *SNCA* levels in the insoluble fraction of *SNCA* O/E hSMAs. While further studies are needed to confirm neural circuitry and synucleinopathy, these results suggest that our hSMAs offer an alternative to *in vivo* studies for PD disease modeling. Through the integration of PD-associated genetic alterations, particularly elevated α-syn expression, our hSMAs manifest PD-like pathology, including damage to the nigrostriatal system. Importantly, we observed the retrograde propagation of α-syn from the striatal to midbrain areas in our hSMAs, accompanied by the accumulation of α-syn aggregates reminiscent of Lewy pathology observed in PD patients. These results highlight the potential of our hSMAs as a valuable platform for elucidating the underlying mechanisms of PD targeting α-syn propagation.

Disclosures: M. Shin: None. **H. Tran:** None. **X. Yeo:** None. **S. Jung:** None. **C. Denman:** None. **M. Kim:** None. **D. Jeon:** None. **H. Kim:** None. **J. Mun:** None. **E. Lee:** None. **S. Park:** None. **B. Kuhn:** None. **G.W. Arbuthnott:** None. **J. Jo:** None.

Poster

PSTR329: Alpha-Synuclein: Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR329.29/C22

Topic: C.03. Parkinson's Disease

Support: PNRR-MAD-2022-12375960
GR-2021-12372698
InflammaPark #1750818

Title: Shifting perspectives: the impact of the immune system on neurodegeneration in parkinson's disease

Authors: *A. CALDERONI[1], S. BIDO[1], M. NANNONI[2,3,4], S. MUGGEO[1], D. GAMBARÈ[1], G. RUFFINI[1], M. LUONI[1,4], M. PROVINCIALI[1], S. G. GIANNELLI[1], V. BROCCOLI[1,4]; [1]San Raffaele Scientific Inst., Milan, Italy; [2]Milano-Bicocca Univ., Milan, Italy; [3]San Raffaele Scientific Institute, Milan, Italy; [4]National Research Council (CNR), Institute of Neuroscience, Milan, Italy

Abstract: Parkinson's Disease (PD) is a neurodegenerative pathology characterized by loss of dopaminergic neurons (DANs) of the substantia nigra, accumulation and aggregation of ***α***;-synuclein (αSYN), and neuroinflammation. Neuroinflammation is a risk factor to PD development, moreover the pathology is characterized by a correlation between levels of proinflammatory cytokines and disease severity, a consistent activation of microglia and recruitment of $CD4^+$ and $CD8^+$ T cells from the perifery since early stages of the disease. Studying the role of neuroinflammation in PD requires establishing its reproducibility across various mouse models, a fundamental step in the research process. Therefore, our group conducted an extensive comparative analysis of the levels of neurodegeneration, microglial activation and T lymphocytes infiltration levels in the substantia nigra pars compacta (SNpc) of different mouse models. These parameters were assessed by tyrosine hydroxylase (TH) staining for DANs counting, immunodecoration for microglial Iba1 activation marker and CD3, CD4 and CD8 to detect lymphocytic infiltrations. Specifically, we studied mice exhibiting pathology through αSYN-induced neurodegeneration. The overexpression of αSYN was obtained by local SNpc administration of αSYN preformed fibrils (PFFs) or delivery of the human wild-type SNCA gene by either lentiviral or adeno-associated viral vectors. Additionally, we utilized Cre-inducible models with DAN or microglial specificity for the expression of αSYN limited to specific cell types. We demonstrated a tight correlation between αSYN accumulation, neurodegeneration and neuroinflammation in most of the models. We also showed that accumulation of αSYN in glial cells rather than in DANs alone determined higher levels of neuroinflammation and neurodegeneration, highlighting the role of these cells in the pathogenic process. Furthermore, microglial activation and T lymphocytes infiltration precedes the loss of DANs in our LV-SNCA mouse model, showing how the immune response and neuroinflammation are key aspects to determine neurodegeneration and the development of the pathology.

Disclosures: A. Calderoni: None. **S. Bido:** None. **M. nannoni:** None. **S. Muggeo:** None. **D. Gambarè:** None. **G. Ruffini:** None. **M. Luoni:** None. **M. Provinciali:** None. **S.G. Giannelli:** None. **V. Broccoli:** None.

Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.01/C23

Topic: I.08. Methods to Modulate Neural Activity

Support: APDA P09
APDA 1053521

Title: Novel approach for enhancing signal recovery during stimulation

Authors: *G. PAIER[1], S. MIOCINOVIC[3], E. OPRI[2];
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Abstract: Deep brain stimulation (DBS) is a neuromodulation-based therapy for neurological disorders that consists of delivering electrical stimuli within specific brain regions for therapeutic benefit. There has been increased interest in leveraging oscillatory and evoked activity to characterize pathophysiological state and spatial information for the optimization of DBS delivery. However, recovering viable electrophysiology from the same electrode is challenging due to large stimulation artifacts and amplifier saturation. This is exacerbated by the limited spatial sampling offered by current electrodes (low number of contacts), requiring techniques able to recover signals during stimulation, including from the stimulating contacts. This work introduces and expands on a novel system, Fully Passive Clipping for Recovering Electrophysiology (FPClipre)[1], designed to mitigate these limitations. Instead of conventional methods based on simple Y-splitter or active switching between the stimulator and recording amplifiers, FPClipre does not require software or complex hardware integration. FPClipre achieves this through 3 stages, the “current limiter stage,” “voltage range limiter stage,” and “stimulation decoupler stage,” to effectively reduce stimulation artifacts while enabling recovery of viable electrophysiology from the same and adjacent contacts post-stimulation (each stimulation pulse). Pilot data from in-vitro testing have shown that FPClipre can recover and maintain signal fidelity with minimal distortion (<0.2%), and importantly avoid any current sinking effect towards the recording amplifier (current loss below 2µA). The passive nature of the FPClipre approach simplifies the integration into existing stimulation-based setups. Further *in vitro* and *in vivo* testing is necessary before the implementation in human studies. This approach has the strong potential to profoundly affect neuromodulation-based research and medical devices by enhancing recovery of pathophysiological and spatial markers directly influenced by stimulation. Additionally, this method is not limited to DBS, and can be leveraged within any setup requiring recording during stimulation. (1) E. Opri and S. Miocinovic, “Recording and recovery of signals during stimulation,” WO2024020212A1, Jan. 25, 2024

Accessed: Mar. 10, 2024. [Online]. Available: https://patents.google.com/patent/WO2024020212A1/

Disclosures: G. Paier: None. **S. Miocinovic:** None. **E. Opri:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Michigan.

Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.02/C25

Topic: I.08. Methods to Modulate Neural Activity

Title: Characterization of Automated Alignment Onboard Fully Implanted Neuromodulation Systems

Authors: *M. O. GOLDSMITH[1], M. E. ALARIE[2], N. R. PROVENZA[4], J. A. HERRON[5], W. F. ASAAD[3];
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Abstract: Recent advancements in deep brain stimulation (DBS) devices have allowed for the concurrent recording of neural data during stimulation, but require a greater degree of validation for the precise synchronization of neural data with behavioral event markers. To mitigate this challenge, previous work by Alarie et al. has developed a method utilizing precisely timed, computer-driven signals to inject artifacts directly into the local field potentials of DBS devices via transcutaneous stimulation (TS). We expanded upon these previously developed alignment tools, characterizing TS and DBS parameters to improve specific device configurations in a more compact system. Round-trip latency for the TS triggering system was determined to be 1.19 ms using a sync-out connection back to task behavioral codes. Benchtop testing was then performed with a Medtronic Percept PC neurostimulator (Medtronic) to compare latencies within our system to inherent device streaming and post-processing latencies. Of particular note, we observed reliable neural-behavioral alignment across TS amplitudes in both Percept Indefinite (relative jitters: 0.5mA: +/- 35.9 ms, 1.5mA: +/- 25.4 ms) and Brainsense Streaming Modes (relative jitters: 0.5mA: +/-45.4 ms, 1.5mA: +/-35.5 ms). Finally, the system was then clinically validated in a patient with DBS of the globus pallidus internus to treat Parkinson's Disease where consistent alignment was only observed at higher TS amplitudes (relative jitter at 1.5 mA: +/- 22.5 ms Brainsense Streaming, +/- 79 ms Percept Indefinite). Ultimately, this work builds on previously developed alignment methods onboard fully implanted systems, providing more extensive best practices for parameters impacting alignment quality.

Disclosures: M.O. Goldsmith: None. **M.E. Alarie:** None. **N.R. Provenza:** None. **J.A. Herron:** None. **W.F. Asaad:** None.

Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.03/C26

Topic: C.03. Parkinson's Disease

Support: NIH R01NS097782

Title: Characterizing Spatio-Spectral Patterns of Oscillatory Power and Connectivity in Parkinson's Disease Patients During DBS Surgery

Authors: *K. MIRPOUR, A. ALIJANPOUROTAGHSARA, M. BENAM, S. CHILUKURI, N. POURATIAN;
UTSW, Dallas, TX

Abstract: The assessment of resting-state functional connectivity has become an essential tool for exploring the underlying mechanisms of Parkinson's Disease (PD). We propose that a unique spatio-spectral pattern of resting functional connectivity between the cortex and basal ganglia serves as a biomarker for the dynamic properties of the motor network. This study investigates the spatial and spectral patterns of oscillatory power and connectivity within and between the cortex and basal ganglia of 30 PD patients during DBS surgery using local field potentials (LFPs) globus pallidus internus (GPi, n=14), subthalamic nucleus (STN, n=17) and electrocorticography (ECoG, n=31) of sensorimotor cortices. To accurately assess the oscillatory components of the neural response, we computed the power spectrum using the Thomson taper method. Subsequently, we fitted a power law model to the spectrum and normalized it to mitigate the influence of the 1/f aperiodic slope. This normalization enabled the precise quantification of the oscillatory components within the spectrum. The results showed that peak oscillatory power in cortical areas was primarily in the beta frequency range. Recordings from the precentral gyrus indicated a peak of power at 20 Hz, with increased amplitude and a narrowing spectrum, slightly shifting to 22 Hz in anterior regions. In contrast, the postcentral gyrus exhibited a broader oscillatory component in the alpha and beta frequencies, peaking at 12 Hz with lower amplitude and wider frequency range toward more posterior regions. In the STN cohort, a robust peak of cortico-basal coherence was centered in the beta frequency range (10 to 35 Hz) anterior to the central gyrus. This coherence pattern was consistent across all STN leads, with minor variations.The coherence pattern spanned the alpha and beta frequency bands in mid-sections of the Pallidum with greater diversity among the pallidum leads. More proximal leads revealed a narrower range within the mid-beta frequency, peaking at 20 Hz and confined to the precentral sulcus. Conversely, distal leads exhibited increased oscillation in the low beta range, peaking at 13 Hz and extending to more anterior cortical areas. Our findings reveal critical oscillatory patterns that enhance understanding of the pathophysiology in movement disorders,

offering a foundation for optimizing DBS targeting and parameters to improve therapeutic outcomes.

Disclosures: K. Mirpour: None. **A. Alijanpourotaghsara:** None. **M. Benam:** None. **S. Chilukuri:** None. **N. Pouratian:** F. Consulting Fees (e.g., advisory boards); Abbott and Sensoria Therapeutics.

Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.04/C27

Topic: C.03. Parkinson's Disease

Title: Volumetric voltage spread around the electrode contact point using a 3D model of subthalamic nucleus (STN): A computational investigation

Authors: *J. NAIK[1], S. S. NAIR[2], P. CHARITHA[2], N. ROHAN[2], S. V. CHAKRAVARTHY[2]; [1]Indian Inst. of Technol. Madras, Chennai, India; [2]Dept. of Biotech., Indian Inst. of Technol. Madras, CHENNAI, India

Abstract: Deep Brain Stimulation (DBS) is an important form of therapeutic intervention used in Parkinson's Disease (PD) patients, especially when the medication efficacy reduces and side effects emerge. DBS effectively suppresses severe motor symptoms such as tremor and rigidity, however few studies have reported negative effects of DBS manifesting as cognitive symptoms such as impulsivity in decision making. This can be attributed to DBS stimulation also affecting the parts of the subthalamic nucleus (STN) that are responsible for cognitive functions, as well as the surrounding space such as the internal capsule. Despite sustained research being conducted in understanding the mechanisms of DBS, one aspect that needs attention is the influence of the DBS current around the electrode contact point on the surrounding structures and medium. For this reason, various modelling efforts are focusing towards understanding the interaction between electrode, extracellular space and the neural activity. In order to pursue this goal, in the present computational study we first start with a 3D anatomical model of STN, taking into account the spatial location of the electrode contact point and the resultant volume of tissue activated (VTA). In this study we model the voltage spread from the electrode contact point across over the STN volume. The volume modelled has a cylindrical geometry with the electrode placed along the center of the cylinder. DBS electrode has four contact leads, each having a length of 1.5 mm and a contact spacing 0.5 mm. The electrode diameter is of 1.27 mm. Distribution of conductivity is assumed to be constant with depth but vary in the plane normal to the axis of the cylinder, as per the experimental data. The basic model (A) used in our study and the preliminary results (C) obtained are as shown in Figure 1. The result in the Figure 1C shows the voltage spread around the contact point in a heterogenous space. This model will be expanded based on diffusion tensor imaging (DTI) data.

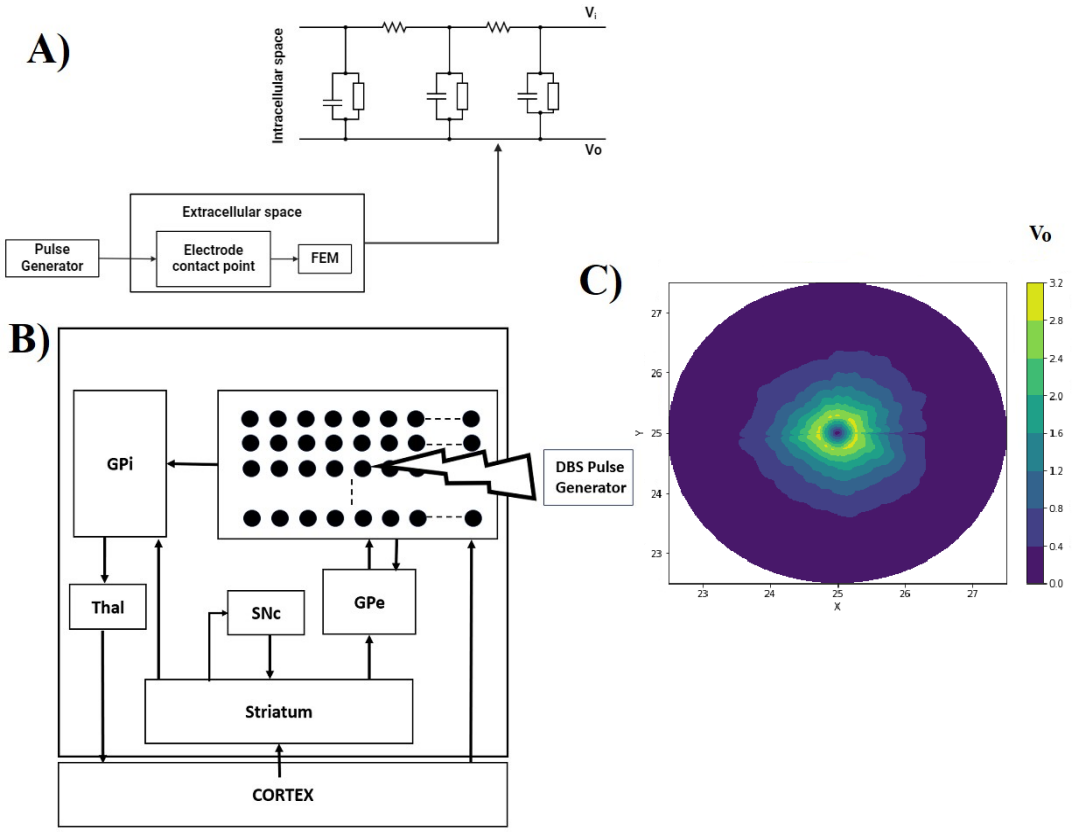

Figure 1. A) The proposed hybrid STN model that combines the extracellular and intracellular characteristics to obtain the membrane potential of the STN neurons. In the current work we have only modelled the extracellular propagation characteristics. B) The representation of the thalamocortical basal ganglia model, where the proposed STN module will be used in the future to study various behavioral functions of the basal ganglia. C) The spread of current obtained after applying the DBS current to the centremost neuron in STN. The colour bar indicates the magnitude of the extracellular Voltage.

Disclosures: J. Naik: None. **S.S. Nair:** None. **P. Charitha:** None. **N. Rohan:** None. **S.V. Chakravarthy:** None.

Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.05/C28

Topic: C.03. Parkinson's Disease

Support: CIHR
NSERC Discovery Grant

Title: Data-driven closed loop deep brain stimulation framework

Authors: S. SARADHI[1], Y. TIAN[1], ***M. LANKARANY**[2];
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Abstract: Motivation: Thalamic ventral intermediate nucleus (Vim) is the primary surgical target of deep brain stimulation (DBS) for reducing symptoms of essential tremor (ET). Closed-loop control of DBS is crucial for effective and automatic treatments of various neurological disorders like Parkinson's disease (PD) and ET. The continuous stimulation in open-loop (manual) DBS may decrease battery life and cause side effects. On the contrary, a closed-loop DBS system utilizes a feedback biomarker to track patient's symptoms and provide stimulations when needed. Existing closed-loop DBS control systems do not incorporate physiological mechanisms underlying the DBS or symptoms. In this work, we developed a model-based DBS control system where a biophysically-reasonable model can describe the relationship between DBS and neural activity, and a deep learning algorithm that can perform the control with a closed-loop controller. Materials and Method: We have access to single-unit recordings of Vim neurons during Vim DBS in human. We developed a macroscopic model connecting DBS, Vim, motor cortex, motor neurons in the spinal cord, and muscle fibers to generate muscle activities, which are represented by EMG. Then we developed a Long Short-Term Memory (LSTM) deep learning model to link Vim-DBS from 5-200Hz range of frequencies to model-predicted EMG signals. The model incorporates the spectral and temporal characteristics of the Vim-DBS and predicted EMG signals as features to model their nonlinear relationship. The LSTM model is used in a proportional-integral-derivative (PID) controller that automatically updates the appropriate DBS frequency in a quasi-real-time manner. Results: Our model-predicted EMG can replicate the essential tremor symptoms during DBS OFF, and is consistent with clinical observations of tremor during different frequencies of Vim-DBS. The closed-loop control system can automatically update the appropriate DBS frequency so that EMG power reaches a desired target. The implemented deep learning model accurately predicts an EMG which corresponds to each input DBS frequency as shown by an R2 value of 0.584. Conclusions: Our closed-loop control system can be potentially implemented in and out of the clinic to automatically update the appropriate DBS frequency.

Disclosures: S. Saradhi: None. **Y. Tian:** None. **M. Lankarany:** None.

Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.06/C29

Topic: C.03. Parkinson's Disease

Support: Retune TRR 295

Title: Beta synhcrony lateralization in Parkinson's Disease stopping network

Authors: *H. POURAKBARI ASLSARDROUD[1], B. AL-FATLY[2], M. SURE[5], A. JHA[6], R. KÖHLER[3], N. LI[4], A. HORN[7], V. LITVAK[8], E. FLORIN[5], A. A. KUEHN[9], W.-J. NEUMANN[10];
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Abstract: Parkinson's disease (PD) is the fastest growing neurodegenerative disorder. Loss of dopaminergic neurons in PD is associated with akinesia. It has been proposed that modulation of a right lateralized stopping network, connecting (pre-)supplementary motor area (preSMA), inferior frontal gyrus (IFG) and subthalamic nucleus (STN) can alleviate akinesia. Indeed, deep brain stimulation (DBS) of the STN has been reported to modulate hyperdirect monosynaptic cortico-subthalamic afferents from preSMA and IFG. One of the putative mechanisms of DBS is the suppression of excessive beta oscillatory synchrony, but to what degree pathological circuit synchrony in the stopping network relates to PD pathophysiology and therapeutic symptom alleviation remains unknown. To address this important research question, we combine normative MRI connectomics with magnetoencephalography and invasive neurophysiology in PD patients undergoing STN-DBS. We provide first evidence that structural connectivity in the stopping network is right lateralized, both in healthy and PD cohorts. Next, we demonstrate that macroscale circuit synchrony, but not local power of beta oscillations follows this lateralization in the stopping network in the hypodopaminergic OFF state in PD patients (n=37, P-Value<0.05). Finally, we demonstrate that dopamine modulates beta synchrony in the right lateralized stopping network. Taken together, our study highlights the importance of this network for the brain circuit architecture of PD pathophysiology and provides new insights to inspire next-generation brain network interventions with neurotechnology.

Disclosures: H. Pourakbari Aslsardroud: None. **B. Al-Fatly:** None. **M. Sure:** None. **A. Jha:** None. **R. Köhler:** None. **N. Li:** None. **A. Horn:** None. **V. Litvak:** None. **E. Florin:** None. **A.A. Kuehn:** None. **W. Neumann:** None.

Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.07/C30

Topic: C.03. Parkinson's Disease

Support: APDA P09
APDA 1053521
Udall Parkinson's Foundation Research Center of Excellence

Title: Deep brain stimulation local evoked potentials to predict therapeutic outcomes in Parkinson's Disease

Authors: *E. BENCE[1], E. GADZIC[2], W. ENGELHARDT[6], N. MANTENA[2], S. MIOCINOVIC[7], P. BRUNNER[6], J. T. WILLIE[8], A. HESTON[3], K. CHOU[3], K. CHEN[4], E. L. LEVIN[9], D. K. LEVENTHAL[3], E. OPRI[5];
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Abstract: Deep Brain Stimulation (DBS) is an established treatment for Parkinson's Disease (PD), yet challenges persist in achieving optimal surgical implantation position and postoperative programming. Approximately 34% of DBS surgeries require revision, highlighting the need for improved techniques (Rolston et al., 2016). The DBS local evoked potential (DLEP) presents a promising avenue for enhancing surgical precision and patient comfort by enabling functional mapping in asleep procedures. We investigated the capacity for DLEP amplitude to predict therapeutic outcomes in PD patients undergoing DBS surgery targeting the globus pallidus internus (GPi) or subthalamic nucleus (STN). Local field potentials were recorded from 31 awake patients and 14 under general anesthesia (GA). We evoked DLEPs with high-frequency (130Hz) and low-frequency (11Hz) stimulation. Post-processing techniques isolated DLEP activity from stimulation artifacts, and postoperative lead localization was performed using image-guided reconstruction with LeadDBS. Our results revealed higher DLEP root mean square envelopes near sensorimotor targets. DLEPs induced within 0.5mm of the dorsal edge of the GPi had significantly higher amplitudes compared to those evoked 1 and 2mm above (p-values: 0.006, 0.002). DLEPs elicited within the STN had higher amplitudes compared to those within 0.25mm of the ventral border while awake (p-value: 0.047) and under GA (p-value: 0.0306). The contact chosen for chronic stimulation corresponded with one of the two contacts eliciting the highest DLEP amplitudes in 75% of awake hemispheres, and with the contact eliciting the highest amplitude in 57.14% of hemispheres. The contacts with lowest effect threshold matched the contacts with highest DLEP amplitudes in 76.19% of hemispheres. Furthermore, STN DLEP amplitudes recovered while awake and under GA were better correlated using high-frequency stimulation (R2: 0.41, p-value: 7.2e-9) compared to low-frequency stimulation (R2: 0.24, p-value: 1.2e-5), suggesting DLEPs may be more spatially consistent with high-frequency stimulation. Our findings show a promising correlation between DLEPs and therapeutic effect in PD, potentially leading to improved targeting and programming strategies and better patient outcomes.

Disclosures: E. Bence: None. **E. Gadzic:** None. **W. Engelhardt:** None. **N. Mantena:** None. **S. Miocinovic:** None. **P. Brunner:** None. **J.T. Willie:** None. **A. Heston:** None. **K. Chou:** None. **K. Chen:** None. **E.L. Levin:** None. **D.K. Leventhal:** None. **E. Opri:** None.

Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.08/C31

Topic: C.03. Parkinson's Disease

Support: Fondation pour la Recherche Médicale FRM Equipe grant
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École normale supérieure, PhD program

Title: Deep brain stimulation restores information processing in parkinsonian cortical networks

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Abstract: Parkinson's disease (PD) is characterized by alterations of neural activity and information processing in the basal ganglia and cerebral cortex, including changes in excitability (Lindenbach and Bishop, 2013; Valverde et al., 2020) and abnormal synchronization (Goldberg et al., 2002; Pollok et al., 2012) in the motor cortex of PD patients and PD animal models. Deep Brain Stimulation (DBS) provides an effective symptomatic treatment in PD (Kalia and Lang, 2015) but its mechanisms of action, enabling the restoration of efficient information transmission through cortico-basal ganglia circuits, remain elusive. A recent theoretical work showed that increased excitability transforms noisy fluctuations into a highly synchronized activity, and that high-frequency stimulation restores physiological activity and increases information processing capabilities (Touboul et al., 2020). Here, we developed a computational framework to test DBS impact on cortical network dynamics and information encoding depending on the network's initial levels of excitability and synchronization. We focused on the response properties of simplified cortical networks to different stimuli, with or without DBS, and especially measured the capacity to decode and discriminate these stimuli based on cortical activity. We first found that DBS efficiently reduces the firing rate in a large spectrum of parkinsonian networks, and in doing so can decrease abnormal synchronization levels. In addition, DBS-mediated improvements of information processing were most exacerbated in synchronized regimes.

Interestingly, DBS efficiency was modulated by the configuration of the cortical circuit such that optimal DBS parameters varied depending on the pathological cortical activity and connectivity profile. We further validated the hypothesis that DBS positively impacts cortical information transmission in the clinics, by investigating whether PD treatment could improve the ability to predict movement from electroencephalograms collected in human parkinsonian patients. The accuracy of decoding movement identity from cortical dynamics was worse when DBS was turned off and correlated with the extent of drug treatment. These last experiments open new perspectives for adaptively tuning DBS parameters, based on clinically accessible measures of cortical information processing capacity. Overall, this work highlights how DBS improves information encoding by resetting cortical networks into highly responsive states. Cortical networks therefore stand as a privileged target for alternative therapies and adaptive DBS.

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Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.09/C32

Topic: C.03. Parkinson's Disease

Support: UH3NS100553
UG3NS130202

Title: Sensorimotor cortex high frequency oscillations better characterize motor symptom severity than beta power during DBS surgery for Parkinson's disease

Authors: *J. JADAPALLI[1,2], J. OLSON[3], Z. IRWIN[4], C. GONZALEZ[3], H. WALKER[5]; [1]Neurol., UAB Neurosci. Grad. Programs, Birmingham, AL; [2]University of Alabama at Birmingham, Birmingham, AL; [3]Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; [4]Neurosurg., Univ. of Alabama at Birmingham, BIRMINGHAM, AL; [5]Neurol., UAB Neurosciences Programs, Birmingham, AL

Abstract: Deep brain stimulation (DBS) lead implant often elicits immediate improvements in contralateral motor symptoms in patients with movement disorders. These temporary benefits arise from physical perturbation of the target tissue by the implanted lead, prior to neurostimulation. Here we investigated alterations in cortical field potential dynamics related to this 'microlesion' phenomenon in 31 consecutive participants undergoing subthalamic nucleus DBS for Parkinson's disease. We recorded field potentials from the hand area of the primary motor cortex both at rest and during repetitive contralateral voluntary and passive upper limb movements. Our analyses correlated (1) baseline spectral power with pre-operative motor symptom severity and (2) changes in spectral power with changes in motor symptoms in response to microlesion. With participants awake and at rest, beta power (13-30 Hz) was highest

in primary motor cortex (M1) versus premotor, primary sensory, and secondary sensory cortices ($p<0.001$, mean M1 peak frequency 21±4 Hz). Beta desynchronization occurred during both passive and voluntary repetitive contralateral upper extremity movements, but was most pronounced during voluntary movements. Notably, pre-operative motor symptom severity measured by Unified Parkinson Disease Rating Scale part 3 total score 'off' medications did not correlate with M1 beta power at rest prior to lead implant ($p=0.41$). Furthermore, motor improvements from microlesion did not correlate with changes in cortical beta power ($p=0.35$). We instead found significant correlations between baseline motor symptom severity and high frequency broadband M1 power (100 - 400 Hz) during repetitive voluntary upper limb movements ($p=0.039$). Furthermore, motor improvements from microlesion correlated with decreases in high frequency broadband power in primary sensory cortex during repetitive passive upper limb movements ($p=0.031$). These findings challenge the hypothesis that beta frequency power in motor cortex is directly linked to motor symptom severity in patients with Parkinson's disease. Instead, our findings suggest closer correlations between motor symptoms and oscillations at higher frequencies, especially at post-central recording sites. Better understanding the spatiotemporal dynamics of cortical field potentials in patients with movement disorders promises to inform novel therapeutic strategies with next-generation adaptive DBS devices.

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Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.10/C33

Topic: C.03. Parkinson's Disease

Support: NINDS R37NS040894
F31 NS130997
Grant from Boston Scientific Corp

Title: Resonance in local- and cortical- evoked potentials from subthalamic nucleus (STN) deep brain stimulation (DBS).

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Abstract: High frequency DBS of the STN reduces the primary motor symptoms of Parkinson's disease (PD). However, DBS programming is a manual, time-consuming process that determines acceptable rather than optimal stimulation parameters. DBS local evoked potentials (DLEPs) and cortical evoked potentials (CEPs) provide insight into the neural responses to DBS pulses. Much remains unknown about the factors which affect DLEP and CEP amplitudes, and these factors

are necessary to understand if evoked potentials are to be used to inform optimal stimulation parameters. We recorded DLEPs and CEPs at DBS frequencies from 40 to 180 Hz during STN lead implantation procedures (n = 8 participants). All study activities were approved by the Duke University Medical Center IRB and all participants provided informed consent.
We first tested frequencies in the therapeutic range (90 - 180 Hz) for 10 s per frequency and 10 s between DBS epochs in 5 participants. DLEP amplitude declined with increasing DBS frequency (Mann-Kendall trend test, $p < 10^{-3}$), and we did not detect resonant responses. However, we have previously observed lower DLEP amplitudes in response to non-therapeutic DBS frequencies (i.e. 45 Hz, Schmidt et al. 2020, Brain Stimulation). We next tested frequencies from 40-180 Hz for 3 s per frequency and 4 s between DBS epochs in 3 participants. The DBS frequency that evoked the largest amplitude DLEPs varied from 80 to 120 Hz between participants. Across participants, we observed a monotonic decrease in DLEP latency with DBS frequency. Cortical evoked potentials did not accommodate to DBS frequency across the extended frequency range (n = 2). Together these data indicate that DLEP amplitude and latency decrease over the therapeutic range of DBS frequency, while CEP amplitude and latency do not. These findings may guide electrophysiology-based programming of DBS parameters and contribute to understanding the mechanisms of DBS.

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Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.11/C34

Topic: C.03. Parkinson’s Disease

Support: NIH Grant DC017718

Title: Speech Outcomes After Deep Brain Stimulation of the Subthalamic Nucleus in Parkinson’s Disease: A Structural and Functional Connectivity Study

Authors: J. VIVANCO SUAREZ[1], F. TABASI[1], A. ROHL[1], S. JEON[1], K. STIPANCIC[2], K. TJADEN[3], D. M. CORCOS[4], C. PATTERSON[5], *J. GREENLEE[1];
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Abstract: Objective: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) in patients with Parkinson’s disease (PD) patients is a well-established surgical treatment that improves motor symptoms and quality of life. However, speech outcomes after STN DBS are variable with previous studies showing deterioration in one-third of implanted patients. Due to

the distant modulation of different neural regions connected to the stimulation site it remains unclear which functional and anatomical connections could explain variable speech changes after DBS. Hence, our objective was to identify the structural and functional connectivity of STN DBS associated with speech changes.
Methods: PD patients with STN DBS were analyzed using open human connectome data (diffusion tractography and resting state functional connectivity) to identify connections associated with changes in a perceptual speech measure (speech intelligibility) at follow-up. Percentage of words accurately transcribed by listeners blinded to stimulation parameters and status was obtained to provide a measure of speech intelligibility. Lead-DBS toolbox was used for lead localization, visualization, and volume of tissue activated (VTA) modeling. Connectivity was assessed using the VTAs as seeds to identify the involved fiber tracts and brain regions.
Results: Functional connectivity between the VTAs and a distributed network of brain regions was measured to determine correlations with speech intelligibility percentage score at follow-up. Furthermore, structural connectivity between VTAs and passing fiber tracks was also assessed for correlation with speech intelligibility percentage score.
Conclusion: Effective STN DBS for PD showed specific connectivity profiles that could potentially predict speech outcomes across independent cohorts. The use of normative connectomes to predict speech outcomes seems to be a valuable tool for individualizing DBS targets and settings. Further research incorporating intraoperative electrophysiological data could enhance the value current imaging techniques for surgical planning and adjustment of the stimulation parameters.

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Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.12/C35

Topic: E.05. Brain-Machine Interface

Support: NIH U24 NS113637

Title: Entrainment of motor cortical beta oscillations during subthalamic deep brain stimulation and voluntary movement in Parkinson’s disease

Authors: *M. SHCHERBAKOVA[1], S. CERNERA[1], A. HAHN[1], S. LITTLE[2], P. A. STARR[1]; [1]Neurolog. Surgery, UC San Francisco, San Francisco, CA; [2]Neurol., UC San Francisco, San Francisco, CA

Abstract: Objective: To study the relationship between cortical finely-tuned gamma (FTG) and beta entrainment via subthalamic nucleus (STN) deep brain stimulation (DBS). **Background:**

Patients with Parkinson's disease (PD) exhibit increased beta band (15-30 Hz) synchronization in the basal ganglia and cortex. This enhanced beta activity is associated with bradykinesia and rigidity in PD, and decreases in response to therapy (dopaminergic medication and high-frequency DBS). STN DBS is hypothesized to facilitate movement by suppressing the "akinetic" beta activity and increasing the "prokinetic" gamma band. We previously showed that therapeutic (>100 Hz) DBS entrains cortical gamma oscillations at half the stimulation frequency. Low-frequency (≤60 Hz) stimulation may induce cortical beta entrainment. **Methods:** We collected field potential data from four hemispheres of three PD patients bilaterally implanted in the STN with an investigational sensing-enabled DBS device connected to quadripolar electrocorticography paddles placed over the sensorimotor cortex. In each hemisphere, we tested a range of frequency (50-180 Hz) and amplitude (0-6 mA) combinations during unilateral stimulation. Patients performed a finger-tapping task with the contralateral hand at each setting. We quantified the degree of neural synchronization present at half the stimulation frequency at each frequency-amplitude combination using the FOOOF algorithm [1], and compared entrainment amplitudes observed during different stages of voluntary movement. Severity of bradykinesia was determined using surface electromyography electrodes and video kinematic analysis. **Results:** In all hemispheres, we observed gamma entrainment during high-frequency (>70 Hz) stimulation, and beta entrainment during low-frequency (≤60 Hz) stimulation. Both types of entrainment occurred at half the stimulation frequency, had higher amplitudes in precentral than postcentral gyrus, and were enhanced with movement. At beta-entraining stimulation frequencies, despite initial beta desynchronization at movement onset, we observed subsequent increase in cortical beta synchronization associated with ongoing movement. **Conclusions:** DBS at ≤60 Hz provides a means of experimentally augmenting cortical beta band synchronization. Analysis of kinematic effects of this intervention will be presented.

[1] Donoghue et al., *Nat. Neurosci.*, 2020

Disclosures: M. Shcherbakova: None. **S. Cernera:** A. Employment/Salary (full or part-time):; Synchron, Inc. since April 2024. **A. Hahn:** None. **S. Little:** None. **P.A. Starr:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); received investigational sensing devices from the manufacturer (Medtronic) at no cost.

Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.13/C36

Topic: E.05. Brain-Machine Interface

Support: NIH GRANT K00NS118719

Title: Long-term sensorimotor cortex sensing using subgaleal leads during deep brain stimulation for Parkinson's disease

Authors: *S. S. SANDOVAL-PISTORIUS[1], R. A. FERNANDEZ-GAJARDO[1], S. CERNERA[1], S. S. WANG[2], D. D. WANG[3], S. LITTLE[4], P. A. STARR[5];
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Abstract: Pathological oscillatory activity in cortico-basal ganglia circuits is linked to motor symptoms in Parkinson's disease (PD). Sensing-enabled deep brain stimulation (DBS) devices connected to subdural electrocorticography (ECoG) leads over sensorimotor cortex show that changes in oscillatory activity across the cortex-BG motor network correlate with motor signs and therapeutic response. Advances in adaptive DBS (aDBS), which adjusts stimulation based on neural signals, requires identification of neurophysiological biomarkers that correlate with various motor symptoms. Cortical biomarkers are promising feedback signals for aDBS, but limited studies exist due to the invasiveness of subdural ECoG paddles. Using less invasive under-the-scalp (e.g., subgaleal) permanent leads to record cortical activity would reduce risks associated with placing permanent electrodes directly on the brain's surface and enable more rapid scalability of aDBS using cortical signals. This study aims to establish the feasibility of long-term subgaleal cortical sensing.
Three individuals with PD were implanted with bilateral sensing-enabled DBS devices, each connected to a directional lead targeting the subthalamic nucleus (STN) and a cortical lead placed in the subgaleal space over sensorimotor cortex. For cortical sensing, an octopolar 10.5 mm cylindrical segmented DBS lead was implanted over one side and an octopolar 57 mm paddle type lead, normally used for spinal cord stimulation, was implanted over the other side. We recorded local field potentials from both the STN and subgaleal leads while the study participant was at rest, during movement tasks, and during stimulation amplitude titration.
We found that both subgaleal leads were able to detect beta band oscillatory activity at rest. During stimulation amplitude titrations both subgaleal leads could detect stimulation-entrained finely tuned cortical gamma at half the stimulation frequency (62.5 Hz). Both subgaleal leads could detect cortical movement-task-related beta desynchronization.
These findings suggest that subgaleal cortical recording can detect sensorimotor activity in physiologically relevant frequency bands. Detection of cortical finely tuned gamma (FTG) activity, a promising feedback signal for aDBS, suggests that subgaleal sensing may be used in studies of aDBS. Ongoing studies are investigating sensorimotor activity during various brain states, including on/off DBS and on/off medication.

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Poster

PSTR330: Deep Brain Stimulation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR330.14/C37

Topic: G.04. Emotion

Support: NIH Grant R01MH119384

Title: Benchtop environment for assessing artifacts generated during current injection

Authors: *J. MORROW[1], S. MILLER[2], J. A. HERRON[3], A. S. WIDGE[2];
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Abstract: The ability to modulate the activity of specific areas or circuits in the human brain offers immense therapeutic potential. For example, the development of deep brain stimulation (DBS) provided the biggest advance in treating Parkinson's Disease since levodopa. While this technique also holds promise for psychiatric disorders like depression or OCD, current success rates leave significant room for improvement. Developing a more complete understanding of how electrical stimulation affects brain circuits would improve our ability to create better treatments; however, performing basic scientific assessments of the impacts of current injection into neural systems is not a simple task. Assembling an electrophysiology rig can be a complicated process that becomes especially frustrating when components from several manufacturers need to work together. The NeuroTest board (NTB) was designed to mitigate these issues by allowing users to test the recording and current delivery capabilities of a broad range of equipment in a benchtop environment.

Here, we describe the NTB setup and assessment of several amplification systems, signal generators, and electrode builds. The NeuroTest board environment itself is low-cost, easy to assemble, and only requires a low-end computer and a saline tank. The system has a signal generator that can output signals at a 10kHz sampling rate and has an input sampling rate of 8kHz, meaning that it is optimized for simulating local field potential oscillations rather than spiking activity. Filter and gain settings can be configured online to mirror parameters being used for in vivo experiments. User friendly, open source software is used to program the signal generator and/or data acquisition components of the NTB. Real data can also be replayed on the board via an SD card and the NTB can be connected to other devices via USB. These features allow users to easily simulate evoked response potentials under a variety of conditions in a controlled environment.

In our testing, we assessed electrical artifacts generated by a StimJim, an A-M Systems analog stimulus isolator (Model 2200), and the signal generator of the NTB. Our amplification systems include two Intan headstages (RHD 2132 and RHD 2164) and a Brownlee multi-channel amplifier (Model 440). Data were recorded via individual platinum-iridium wires or linear arrays (Neuronexus or Polymer Implantable Electrode Foundry). Both the NTB and an OpenEphys board were used for data acquisition. Taken together, these tests demonstrate how the NTB can be used to directly compare similar pieces of equipment, as well as isolate and address artifacts such as amplifier saturation or line noise.

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Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.01/C38

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Safety liabilities of huntingtin loss

Authors: R. IMMONEN[1], ***T. HEIKKINEN**[2], Y. SINGH[2], T.-K. STENIUS[2], L. RAUHALA[2], M. MUTIKAINEN[2], M. YACOUB[2], T. MIETTINEN[2], I. NNAH[3], M. HIRST[4], H. TANG[5], R. CHEN[6], D. HOWLAND[5], D. M. MARCHIONINI[5];
[1]Charles River Discovery Res. Services, [2]Charles River Discovery Res. Services, Kuopio, Finland; [3]Charles River Discovery Res. Services, Shrewsbury, MA; [4]Rancho Biosci., San Diego, CA; [5]CHDI Management, Inc. for CHDI Foundation, Inc.,, New York, NY; [6]CHDI Management, Inc. for CHDI Foundation, Inc., New York, NY

Abstract: A number of Huntingtin (*HTT)* lowering reagents have entered or are entering clinical trials as a therapeutic strategy for Huntington's disease (HD). *HTT* is expressed in all cells in the body and its function has been implicated in numerous mechanisms. We utilized a mouse model with conditional loss of HTT.
LoxP sites were inserted at 1356 bp 5' from the start of exon 1 and 2150 bp 3' from the end of exon 1 (in intron A) in the Q20 knockin mouse to generate cHtt-Q20 mice, which were crossed to UBC-Cre^{ERT2} to generate Htt-Q20$^{2lox/2lox}$;UBC$^{cre/+}$ progeny (cQ20). Young adult mice were treated with vehicle or tamoxifen (TM) at 12 weeks of age to induce cre-mediated recombination and global excision of HTT.
In the brain, there was no measurable unintended cre recombination in the absence of TM, and greater than 70% bulk loss of HTT after TM administration.
After 4 weeks of HTT loss, volumetric MRI revealed a reduction in striatal and thalamic volume, while no MRS changes were identified. Mice exhibited a robust increase in neurofilament light chain (NFL) in both plasma and CSF. Mice also exhibited neuroinflammatory astrocytes, as measured by GFAP-immunoreactivity, most robustly in the spinal cord and thalamus.
Preliminary analysis of SnSeq analysis of the cortex revealed transcriptional dysregulation across multiple cell types identified in the cortex; many previously identified HD-related pathways were similarly dysregulated when differential gene expression changes between control and TM-treated mice were examined. Overall, total HTT loss led to a number of measurable changes and should be taken into account when considering pan- HTT lowering therapeutics.

Disclosures: R. Immonen: A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **T. Heikkinen:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **Y. Singh:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **T. Stenius:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **L. Rauhala:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **M. Mutikainen:** A. Employment/Salary

(full or part-time):; Charles River Discovery Research Services. **M. Yacoub:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **T. Miettinen:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **I. Nnah:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **M. Hirst:** A. Employment/Salary (full or part-time):; Rancho Biosciences. **H. Tang:** A. Employment/Salary (full or part-time):; CHDI Management, Inc. for CHDI Foundation, Inc.,. **R. Chen:** A. Employment/Salary (full or part-time):; CHDI Management, Inc. for CHDI Foundation, Inc.,. **D. Howland:** A. Employment/Salary (full or part-time):; CHDI Management, Inc. for CHDI Foundation, Inc.,. **D.M. Marchionini:** A. Employment/Salary (full or part-time):; CHDI Management, Inc. for CHDI Foundation, Inc.,.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.02/C39

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: FRQS Master's Training Bursary

Title: Implication of small non-coding RNAs in Huntington's Disease

Authors: *G. BOULAY[1], S. S. HEBERT[2];
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Abstract: Huntington's disease (HD) is an incurable neurodegenerative disorder characterized primarily by the degeneration of striato-cortical neurons, leading to the progressive loss of cognitive function and motor control. The disease is caused by a mutation in the gene coding for the Huntingtin (HTT) protein which leads to its aggregation and early transcriptional changes. We and others have shown that microRNA expression and maturation are strongly impaired in HD. Whether other classes of small regulatory RNAs are affected in HD remains poorly documented. Since non-coding RNAs can regulate transcriptional, translational and splicing processes, we hypothesized that other types of non-coding RNAs would also be deregulated in HD. In this study, we aim to characterize the expression of non-coding RNAs during HD progression, focusing on small nucleolar RNAs (snoRNAs) and small nuclear (snRNA), among other types of regulatory small RNAs. SnoRNAs are 60-300 nt non-coding RNA sequences, divided into two groups that respectively guide rRNA and snRNA methylation (SNORD) and pseudouridylation (SNORA), thereby promoting ribosomal and snRNA maturation. They are also precursors for miRNA-like fragments (17-30 nt) having mRNA silencing capabilities. SnRNAs are 150 nt ncRNA sequences that are integral parts of the spliceosome and are necessary for spliceosomal assembly and function.
Here, we analyzed a small RNA-sequencing dataset of human BA-9 cortices obtained from Gene Expression Omnibus (Hoss et al., 2015) in order to identify non-coding RNA biotypes that could

be involved in the progression of HD. We found that SNORAs and SNORDs are differentially dysregulated in HD. SNORDs are strongly upregulated in HD3 but not in other stages. For their part, SNORAs are initially globally upregulated at an early stage of the disease (HD2), with a shift occurring that leads to their downregulation in later stages (HD3 and HD4). SnRNA expression highly resembles SNORA expression pattern, with an early upregulation followed by a latter downregulation. Since mutant HTT is known to interact with RNA-binding proteins in the nucleus, our results suggest that snoRNA and snRNA-binding ribonucleoproteins could interact with mutant Huntingtin protein aggregates, contributing to transcriptional, translational and splicing defects observed in HD.

Disclosures: G. Boulay: None. **S.S. Hebert:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.03/C40

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Modeling Huntington's disease in iPSC-derived medium spiny neurons identified a potential therapeutic agent in vitro.

Authors: *S. YOSHIDA[1], H. KOKUBU[1], T. KAWAGUCHI[1], H. ASANO[1], M. YANO[2,3], K. FUKUSHIMA[1], H. OKANO[4,3];
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Abstract: Introduction: Huntington's disease (HD) is an autosomal-dominant late-onset neurodegenerative disease clinically characterized by progressive movement symptoms including chorea, cognitive impairment, and psychiatric symptoms, for which no effective therapeutic agent is available. HD is caused by an abnormally long CAG repeat tract in exon 1 of the Huntingtin gene (*HTT*) which results in the accumulation of abnormal HTT protein aggregates during adulthood. The neuropathology of HD is primarily the selective degeneration of dopamine receptor D2-expressing (DRD2+) medium spiny neurons (MSNs) in the striatum. In this study, we established *in vitro* cell model of DRD2+ MSNs differentiated from HD patient-derived induced pluripotent stem cells (iPSCs) and screened for small compounds that mitigates the several phenotypes in this cell model. Method: Using a Tet-On-inducible transcription factor expression system carried on the PiggyBac vector, we efficiently generated MSNs from HD patient-derived iPSCs (CAG repeat length 180, 50, 47, representatively) to establish disease-specific phenotypic systems. To characterize MSNs, we examined immunocytochemical markers which are DARPP32 as MSN marker and DRD1 and DRD2 as MSN subtype markers. To identify neuronal death, we performed the LDH leakage assay. In addition, we combined anti-HTT (MAB5374) with anti-poly-glutamine (1C2) antibodies to detect aggregated HTT

accumulation in the nucleus (DAPI). To screen drug candidates for disease modification, a commercially available 1,269 compound library was employed. Result: HD patient derived neurons had nearly 90% of DARPP32-positive population similar to healthy controls, where most of neurons also were DRD2-positive. To examine disease-specific phenotypes, we performed an LDH leakage assay using supernatant from day 8 to day 34. HD-MSNs showed more LDH leakage than healthy controls after day 21 and significantly increased LDH leakage on day 34 ($p=0.0007$, One-way ANOVA). At the same time, we compared neurite length and aggregated HTT of HD-MSN and healthy controls. The neurite length of HD-MSNs had more shortened neurites than that of healthy controls ($p=0.001$, One-way ANOVA). HD-MSNs also showed increased HTT aggregation compared to healthy controls ($p=0.0001$, One-way ANOVA). Based on those results, we performed phenotypic screening using 1,269 compounds and found 8 compounds that rescued neurite length shortening, cell deaths and HTT aggregation. Conclusion: DRD2+ MSNs from HD patients showed disease phenotypes *in vitro* and revealed therapeutic agents for HD. Currently, we investigate the underlying mechanism of one of those drug candidates.

Disclosures: S. yoshida: A. Employment/Salary (full or part-time):; K Pharma, Inc. **H. Kokubu:** A. Employment/Salary (full or part-time):; K Pharma, Inc. **T. Kawaguchi:** A. Employment/Salary (full or part-time):; K Pharma, Inc. **H. Asano:** A. Employment/Salary (full or part-time):; K Pharma, Inc. **M. Yano:** A. Employment/Salary (full or part-time):; K Pharma, Inc.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; K Pharma, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); K Pharma, Inc. **K. Fukushima:** A. Employment/Salary (full or part-time):; K Pharma, Inc.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; K Pharma, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); K Pharma, Inc. **H. Okano:** A. Employment/Salary (full or part-time):; K Pharma, Inc.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; K Pharma, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); K Pharma, Inc..

Poster

PSTR331: Huntington’s Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.04/C41

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Physiologically relevant media unmasks severe mitochondrial dysfunction in a deterministically programmed iPSC-derived model of Huntington's disease

Authors: C. MONTEITH[1], T. OOSTERVEEN[2], L. FOULSER[1], S. POKORNY[1], M. GAMPERL[3], S. SALIC-HAINZL[3], T. BUERCKSTUEMMER[3], *A. TURNER[1], O. DOVEY[1], W. BERNARD[1], E. METZAKOPIAN[1], M. KOTTER[1];
[2]CTD, [1]bit.bio, Cambridge, United Kingdom; [3]bit.bio, Vienna, Austria

Abstract: Huntington's disease (HD) is a devastating disease characterised by degeneration of the medium spiny neurons (MSNs) in the striatum. HD patients suffer from uncontrollable movements as well as severe mental problems and currently no disease modifying treatments are available. HD is an autosomal dominant disorder caused by a CAG repeat expansion encoding an elongated polyglutamine (PolyQ) stretch in the Huntingtin (HTT) protein. Although the precise pathogenic mechanisms remain poorly understood, the mutant aggregation prone HTT protein has been reported to affect various cellular processes, including the biogenesis, fission, transport and respiration of mitochondria. HTT is ubiquitously expressed in the brain and, albeit MSNs are the most susceptible neurons to the toxic effects of mutant HTT protein, other neuronal subtypes such as the cortical glutamatergic neurons are affected during later disease stages. We developed a novel iPSC-derived HD model based on our ioGlutamatergic Neurons™ that have been generated utilising opti-ox™ deterministic cell programming. These ioGlutamatergic Neurons HTT 50CAG/WT contain a genetically engineered heterozygous 50 CAG repeat expansion in exon 1 of Huntingtin. To investigate mitochondrial function in our HD model, cells were cultured in Neurobasal medium for 11 days and analysed with a Seahorse assay. The HD model showed a significant but modest reduction in basal and ATP-linked respiration relative to the genetically matched wild type control. Unexpectedly, at day 25 oxygen consumption rates in both genotypes were highly similar as neurons switched from mitochondrial respiration to glycolysis. Interestingly, culturing cells in a more physiologically relevant medium supported mitochondrial respiration at day 25 and unmasked a dramatic and significant mitochondrial dysfunction in the HD model. As neuronal firing is energy demanding, we assessed by high-resolution MEA recordings whether mitochondrial dysfunction in the HD model affects neuronal activity relative to wild type cells. Culturing the cells over 30 days in a physiologically relevant media significantly decreased the firing amplitude and rate as well as network activity in the HD model. Overall, we have developed a scalable and consistent human HD model that recapitulates critical disease aspects and enables disease mechanistic and drug discovery studies.

Disclosures: C. Monteith: None. **T. Oosterveen:** None. **L. Foulser:** None. **S. Pokorny:** None. **M. Gamperl:** None. **S. Salic-Hainzl:** None. **T. Buerckstuemmer:** None. **A. Turner:** None. **O. Dovey:** None. **W. Bernard:** None. **E. Metzakopian:** None. **M. Kotter:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.05/C42

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Robert W. & Eleanor H. Biggs Endowed Professor of Neuroscience (G.F.K)

Title: Agrochemical Dieldrin and Mutant HD Cooperatively Promote Oxidative Stress and Reduce Mitochondria Health and Function in a Striatal Cell Model of Huntington's Disease

Authors: *P. GONZALEZ[1], M. MOON[1], S. ROBINSON-CLOETE[1], T. ZANA[1], W. MULIAWAN[1], G. F. KWAKYE[2];
[1]Neurosci., Oberlin Col., Oberlin, OH; [2]Neurosci. Dept., Room K232, Oberlin Col., Oberlin, OH

Abstract: Exposure to environmental toxicants such as heavy metals and pesticides can induce neurotoxicity and cell death in Huntington's disease (HD), contributing to disease severity. The organochloride pesticide dieldrin (DLD) has been reported to accumulate in post-mortem brain tissue; DLD has been shown to induce neurotoxicity through oxidative stress and alter mitochondria health and protein degradation pathways in Parkinson's disease (PD). Recognizing the similar pathophysiological mechanism between PD, HD, and pesticide exposure, we hypothesize that expression of mutant Huntingtin protein coupled with acute exposure to DLD will promote neurotoxicity and neurodegeneration via oxidative stress-mediated mitochondria and protein dysfunctional pathways. Utilizing an established immortalized striatal cell model of HD (Wild-type $STHdh^{Q7/Q7}$, Mutant $STHdh^{Q111/Q111}$), we report that mutant cells are significantly more susceptible to acute DLD-induced neurotoxicity compared to wild-type upon 24-hour exposure. Biochemical analysis of mitochondria health following 100µM DLD exposure revealed a time-dependent reduction in mitochondrial membrane potential and ATP production in mutant cells compared to wild-type. To further elucidate the molecular mechanisms underlying mutant and DLD-induced neurotoxicity, we performed immunoblotting analysis that showed a reduction in oxidative stress-related protein expression, including KEAP1 and Nrf2, and an increase in SOD1, SOD2, and NQO1 protein levels. DLD significantly increased proteasomal activity in wild-type and mutant cells compared to baseline controls, suggesting impaired proteasomal activity. Our findings indicate that mutant and DLD negatively impact oxidative stress, mitochondria function, and proteasomal activity in striatal cells, resulting in neurotoxicity and neurodegeneration. These findings are relevant to educating at-risk populations and developing therapeutic approaches in HD.

Disclosures: P. Gonzalez: None. **M. Moon:** None. **S. Robinson-Cloete:** None. **T. Zana:** None. **W. Muliawan:** None. **G.F. Kwakye:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.06/C43

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Robert W. & Eleanor H. Biggs Endowed Professor of Neuroscience (G.F.K)

Title: Methylene blue attenuates 3-NPA induced mitochondrial dysfunction in striatal cells: therapeutic implications in Huntington's Disease pathology

Authors: *H. K. HALE[1], K. M. ELIAS[2], S. T. HO[2], A. OROZCO[2], G. F. KWAKYE[3]; [1]Oberlin Col., Oberlin College, OH; [3]Neurosci. Dept., [2]Oberlin Col., Oberlin, OH

Abstract: There are no disease-modifying treatments available for Huntington's disease (HD), a neurodegenerative disease caused by a genetic mutation in the Huntingtin gene. This mutation results in a polyglutamine expansion of the Huntingtin protein (HTT), inducing a host of responses, including progressive loss of neurons in the striatum and other brain regions. Previous research suggests that disruptions in the bioenergetics of the mitochondria and increased oxidative stress are potential inducers of HD. Therapeutics that enhance antioxidant pathways intend to target and attenuate the overproduction of reactive oxygen species that is associated with mitochondrial dysfunction. We have investigated the effect of Methylene Blue (MB) as a potential therapy for HD. MB is a small molecule demonstrated to exhibit neuroprotective effects in other neurodegenerative disease models, including Parkinson's and Alzheimer's, by attenuating the oxidative stress pathways implicated in their pathophysiology. We used an established striatal cell model of HD expressing wild-type ($STHdh^{Q7/Q7}$) or mutant ($STHdh^{Q111/Q111}$) HTT and a chemical inducer of HD, 3-Nitropropionic acid (3-NPA), to determine the HD-specific mechanisms regulated by 3h MB pre-treatment. Upon 24h exposure to 3-NPA, mutant HD cells exhibited a significant concentration-dependent decrease in cell survival and a concomitant increased cell death compared to wild-type, confirming that 3-NPA exacerbates mutant HTT neurotoxicity. Examination of mitochondrial membrane potential by JC-1 assay revealed MB mediated neuroprotection against 3-NPA-induced reduction in mitochondria activity. We observed that MB restores baseline expression of oxidative-stress related proteins, including HO1 and p62 in both wild-type and mutant cells exposed to 3-NPA. A similar effect is observed with mitochondrial biogenesis proteins OPA1 and DRP1. Our findings establish a novel neuroprotective role of MB in both genetic and chemical models of HD, suggesting that MB might be a promising therapeutic candidate for altering the underlying pathophysiology of HD by improving mitochondrial function.

Disclosures: H.K. Hale: None. **K.M. Elias:** None. **S.T. Ho:** None. **A. Orozco:** None. **G.F. Kwakye:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.07/C44

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Canadian Institutes of Health Research grant PJT-185885 to LAR
CIHR Canada Graduate Scholarships-Master's to KT

Title: Characterizing circuit dynamics of sensory learning in a mouse model of Huntington's disease with mesoscale microscopy

Authors: *K. TRAPPENBERG[1,2], J. P. MACKAY[3], D. RAMANDI[3], L. A. RAYMOND[3];
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Abstract: Huntington's disease (HD) is a neurodegenerative disorder that affects numerous brain functions, but the impact of altered sensory processing on sensory cue-based learning in HD remains poorly understood. Previously we performed wide-field mesoscale imaging of anesthetized Q175-GCaMP6s mice with a cranial window and found that sensory stimulation induced spread of cortical activity that included more brain regions and persisted for a longer duration compared to wildtype (WT) littermates. Further experiments on 7- to 9-month-old awake mice produced similar results. These results suggest that sensory processing networks of visual stimuli may be altered in Huntington's disease. Additionally, previous studies have reported a visual learning deficit in a go/no-go discrimination task. As such, we hypothesize that the lack of precise activation of cortical sensory association areas in HD mice may interfere with the accurate encoding of learned information. To test this, we designed a visual discrimination learning task where the mice must distinguish between a single or double LED pulse to receive a reward. Furthermore, our task design involves pairing the stimuli to a conditioned response, allowing investigation of the effects of sensory spread on simple associative learning. During this learning task, we are monitoring the change in network connectivity and circuit functions, thereby determining the behavioural relevance of sensory spread. We analyzed data using both conventional calcium signal methodologies and machine learning attentional networks. Preliminary data shows increased V1 activation in HD mice in response to visual stimuli compared to WT. We also observed a strong brain-wide response to spouts moving toward them during reward presentation, which was more prominent in HD mice. Finally, as the mice learn to associate the task, the brain activity becomes less spread or sustained, especially in WT mice. Together, results of these experiments will increase understanding of the behavioral consequences of altered cortical sensory processing in HD.

Disclosures: K. Trappenberg: None. **J.P. Mackay:** None. **D. Ramandi:** None. **L.A. Raymond:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.08/C45

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI fundation

Title: Hyperactivity of indirect pathway striatal projection neurons in the Q175 mouse model of Huntington's disease.

Authors: *E. LARA-GONZALEZ, J. W. CALLAHAN, M. D. BEVAN;
Neurosci., Northwestern Univ., Chicago, IL

Abstract: Huntington Disease (HD) is an autosomal dominant neurodegenerative disorder caused by the expansion of CAG repeats in exon 1 of the huntingtin gene. HD is characterized by the progressive degeneration of the basal ganglia and cerebral cortex and subsequent psychomotor dysfunction. Although degeneration of basal ganglia and cortex is increasingly widespread with disease progression, neurons in the indirect pathway of the basal ganglia exhibit the earliest and most profound susceptibility. Prior to frank cell loss, indirect pathway neurons exhibit numerous cellular and synaptic changes in HD. However, the impact of these alterations on circuit activity remains poorly understood. To address this gap, we compared the activity of optotagged indirect pathway striatal projection neurons (iSPNs) in 8-10-month-old head-fixed male and female and WT mice during rest and spontaneous self-initiated locomotion on a linear treadmill. At this age, Q175 HD mice exhibit subtle but consistent motor and cognitive deficits compared to their WT counterparts. ChR2(H134R) was specifically expressed in the iSPNs of A2A-Cre X Q175/WT mice using Cre-dependent approaches. iSPNs were optotagged and recorded using 64-channel silicon optrodes. We found that iSPNs are profoundly hyperactive in Q175 vs their WT counterparts at rest and immediately before, during, and after locomotion. We are currently determining whether this abnormal activity can be ameliorated through suppression of mHTT expression in iSPNs using Cre-dependent viral expression of a zinc finger protein-transcriptional repressor that targets the expanded CAG repeat. We found that the hyperactivity of iSPNs in Q175 mice was substantially ameliorated by ZFP expression in iSPNs alone. Together, this research will inform our understanding of the cell-autonomous and circuit mechanisms that underlie psychomotor dysfunction in HD and the therapeutic effectiveness of viral-based selective mutant huntingtin lowering strategies.

Disclosures: E. Lara-Gonzalez: None. **J.W. Callahan:** None. **M.D. Bevan:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.09/C46

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH/NINDS- 5R01NS089750-08
The Dixon Family Foundation

Title: Striatal astrocyte and interneuron activity revelations from a mutant huntingtin mouse model

Authors: *J. S. HAIRSTON[1], M. GRAY[2];
[1]Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; [2]Neurol., Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: Huntington's disease (HD) is a rare neurodegenerative disease caused by a CAG trinucleotide repeat expansion in the Huntingtin gene resulting in an expansion of a polyglutamine repeat in the Huntingtin protein. HD results in degeneration of striatal medium spiny neurons (MSNs). The MSNs are controlled by extrinsic glutamatergic input from cortex and thalamus, extrinsic GABAergic input, and intrinsic inhibitory input from striatal GABAergic interneurons, particularly somatostatin-expressing interneurons (SST-INs) and parvalbumin-expressing interneurons (PV-INs). The balance of input onto the striatal MSNs ensures their proper function which impacts the various striatal circuits that contribute to motor, limbic, and cognitive activities. Astrocytes are also important contributors to the striatal circuit. Striatal astrocytes respond to GABA application as well as endogenous GABAergic activity with Ca2+ elevations. In cortex, astrocytes are more sensitive to SST-IN activity than PV-IN activity. Astrocytic Ca2+ responses strengthened when evoked by SST-IN stimulation and weakened when evoked by PV-IN stimulation. In hippocampus, astrocyte activity was shown to enhance SST-IN inhibition of pyramidal neurons. This response was not seen in PV-INs. However, the interaction of PV-Ins and SST-INs and astrocytes have yet to be studied in striatum. In this work we used aged BACHD mutant huntingtin expressing mouse model displaying motor abnormalities, and wildtype mice to explore astrocytic Ca2+ elevations in the striatum. We use AAV5-gfaABC1D-cyto-GCaMP6f to measure Ca2+ signals and in preliminary experiments we observe alterations in Ca2+ signals in BACHD astrocytes. Furthermore, we have bred SST-Cre and PVB-Cre mice with Ai32 Cre-dependent Channelrhodopsin (ChR) expressing mice and injected them with AAV5-gfaABC1D-cyto-GCaMP6f to explore responses of astrocytes to SST and PVB interneuron activation. We show cell type specificity of expression of ChR in SST and PVB interneurons and we also present preliminary data demonstrating astrocytic responsiveness to SST and PVB interneuron stimulation. Together, these experiments reveal fundamental interactions of striatal astrocytes and interneuron populations and striatal astrocytic Ca2+ changes in the aged BACHD mutant huntingtin expressing mouse model.

Disclosures: J.S. Hairston: None. **M. Gray:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.10/C47

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI (to Gerardo Morfini)
NINDS R21NS096642 (to Gerardo Morfini)

Title: A contribution of the protein kinase JNK3 to deficits in corticostriatal connectivity elicited by mutant huntingtin in vivo.

Authors: *M. PRIEGO LUQUE[1], E. ARTUR DE LA VILLARMOIS[2], E. FLORES-BARRERA[3], H. ZAKY[4], K.-Y. TSENG[5], G. A. MORFINI[3];
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Abstract: Huntington's disease (HD) is an autosomal-dominant monogenic neurodegenerative disorder caused by mutations that result in abnormal expansion of a polyglutamine stretch in the protein huntingtin (HTT). Despite its ubiquitous expression throughout the brain, selected populations of striatal and cortical neurons are the most vulnerable to the disrupting effects of mutant huntingtin (mHTT) protein. The precise molecular mechanisms by which mHTT differentially affect specific neuronal populations to drive the progressive loss of corticostriatal connectivity observed in HD remain unknown. We previously showed toxic effects of mHTT in axons, which were mediated by the cJun-amino terminal kinase (JNK) isoform JNK3. To explore potential contributions of this kinase to HD neuropathology *in vivo*, we evaluated how ubiquitous JNK3 deletion impacts well-established electrophysiological, histological and behavioral alterations of R6/2 mice, a well-established HD model. Collectively, results from this work suggest an important role of JNK3 to corticostriatal disconnection in R6/2 mice, calling for studies designed to illuminate mechanisms by linking mHTT to aberrant activation of the JNK kinase pathway.

Disclosures: M. Priego Luque: None. **E. Artur De La Villarmois:** None. **E. Flores-Barrera:** None. **H. Zaky:** None. **K. Tseng:** None. **G.A. Morfini:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.11/C48

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH/NINDS- 5R01NS089750-08
Dixon Family Foundation

Title: Somatostatin Interneuron Involvement in the Pathogenesis of Huntington's Disease

Authors: *J. A. R. FOWLER[1], M. SCARDUZIO[2], M. GRAY[3];
[1]The Univ. of Alabama at Birmingham, Birmingham, AL; [2]Neurol., UAB, Birmingham, AL;
[3]Neurol., Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: Huntington's disease (HD) is a fatal neurodegenerative disease that is caused by expansion of the CAG tract in exon 1 of the gene encoding the Huntingtin protein. The resulting abnormal polyglutamine-containing protein is ubiquitously expressed, primarily causing striatal degeneration. HD patients have motor, cognitive and psychiatric abnormalities. Striatal degeneration is accompanied by electrophysiological dysfunction of specific cell types. Striatal medium spiny neurons (MSNs) are the primary cell types lost. These cells are modulated by various interneuron populations, one of which is the somatostatin-expressing interneuron (SST+). To study cellular contributions to HD, we utilize conditional BACHD mice, which express a full-length human mutant huntingtin gene (mHTT). Interestingly, these cells are not lost in HD patients as well as in BACHD mice but have increased spontaneous firing. In BACHD mice we also see increased striatal extracellular GABA (e[GABA]) via *in vivo* microdialysis. It is possible that increased SST+ cell firing contributes to the increase in striatal e[GABA]. Understanding the role mHTT expression plays in these cells can provide insight into the dysfunction observed in the striatum of HD patients. We will use a genetic approach to decrease mHTT expression in SST+ cells by crossing BACHD mice to SST-Cre mice, and will assess neuropathological, behavioral, and electrophysiological abnormalities. We hypothesize that expression of mHTT in SST+ influences the increased GABAergic changes observed in MSNs, motor and psychiatric abnormalities and the e[GABA]. Motor dysfunction is not improved in BACHD/SST-Cre mice. Additionally, we prove that the increased spontaneous firing of SST+ cells is cell autonomous.

Disclosures: J.A.R. Fowler: None. **M. Scarduzio:** None. **M. Gray:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.12/C49

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: 5R01 NS101958-06

Title: Estrogen-related receptor gamma is a regulator of mitochondrial, autophagy, and immediate early gene programs in spiny projection neurons: Relevance for neuronal vulnerability in Huntington Disease

Authors: S. N. FOX, N. AMIREDDY, M. GRAY, ***R. M. COWELL**;
Neurol., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Mitochondrial dysfunction, transcriptional dysregulation, and protein aggregation are hallmarks of multiple neurodegenerative disorders, including Huntington's disease (HD). Strategies are needed to counteract these processes to restore neuronal health and function in HD. Recent evidence indicates that the transcription factor estrogen-related receptor gamma (ERRγ/*Esrrg*) is required for normal expression of mitochondrial, synaptic, and autophagy genes in neurons. Further, overexpression of *Esrrg* in dopaminergic neurons reduces synuclein load in the pre-formed fibril model of synucleinopathy. For these reasons, we sought to understand ERRγ's role in transcriptional regulation in spiny projection neurons (SPNs), one of the neuronal populations vulnerable to transcriptional dysregulation, mitochondrial dysfunction, and protein aggregation in HD. Here, we demonstrate that developmental deletion of *Esrrg* selectively in SPNs causes a loss of both *Drd1+* and *Drd2+* populations in the mouse striatum. Given the neuronal loss observed with developmental deletion and our overarching goal to understand *Esrrg*'s role within adult SPN populations, we deleted or overexpressed *Esrrg* in adult SPNs. While overexpression was sufficient to increase the expression of mitochondrial and autophagy-related transcripts, RNA sequencing of *Esrrg*-deficient mice revealed increases in the expression of immediate early genes. In contrast, these genes were downregulated by *Esrrg* overexpression. Concordantly, *Esrrg*-deficient mice exhibited reduced ambulatory responsivity and lack of induction of immediate early genes in response to amphetamine. To determine whether the alterations observed with ERRγ modulation have any relevance for understanding SPN vulnerability in neurodegeneration, we measured *Esrrg* and its responsive genes in two mouse models of HD. We found an increase in *Esrrg* expression in HD models, accompanied by an immediate early gene transcriptional profile similar to what is observed with *Esrrg* overexpression. Altogether, these studies suggest that ERRγ is a key activator of mitochondrial and autophagy-related transcripts in SPNs, with a bi-functional role as a repressor of immediate early genes. Ongoing studies are investigating mechanisms underlying ERRγ's roles in transcriptional activation and repression in SPNs to inform strategies to promote neuroprotective actions of ERRγ in SPNs in HD.

Disclosures: S.N. Fox: A. Employment/Salary (full or part-time):; University of Alabama at Birmingham. **N. Amireddy:** None. **M. Gray:** A. Employment/Salary (full or part-time):; University of Alabama at Birmingham. 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.; National Institutes of Health. **R.M. Cowell:** A. Employment/Salary (full or part-time):; University of Alabama at Birmingham. 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.; National Institutes of Health. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); University of Alabama at Birmingham Impact Funds. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Trialtus Bioscience. F. Consulting Fees (e.g., advisory boards); Acelot, Inc..

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.13/C50

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Internal funds from the Burnett School of Biomedical Sciences

Title: Alterations in hypothalamic dopaminergic neuron expression and distribution in the Q175FDN mouse model of Huntington's Disease

Authors: S. R. MOLDENHAUER, S. LIPKIN, A. L. SOUTHWELL, *B. FRY;
Burnett Sch. of Biomed. Sci., Univ. of Central Florida, Winter Park, FL

Abstract: Huntington's disease (HD) is a neurodegenerative condition marked by a cascade of motor, cognitive, and psychiatric challenges, all stemming from expansions in the huntingtin (HTT) gene. While the pathology of HD predominantly involves the loss of GABAergic medium spiny neurons in the striatum leading to disorders of movement, another symptom that has received less attention involves alterations in circadian feeding behaviors. The hypothalamus serves as a hub for anorexigenic and orexigenic neuropeptides, some of which may be modulated via dopaminergic circuitry. This in mind, we utilized a combination of immunohistochemistry and topological data analysis to examine differences in expression and distribution of putative dopaminergic neurons within the hypothalamus of Q175FDN HD mice as compared to wild-type. We found a significant increase in the number of tyrosine-hydroxylase positive cells in the arcuate nucleus of the hypothalamus (ARC) of Q175FDN mice, indicating a potential connection between dopaminergic signaling within the ARC and some non-motoric symptoms (e.g., alterations in feeding) seen in HD. Using topological data analysis, we also found differences in the shape of the data concerning spatial distribution of dopaminergic neurons in the model. These data add further evidence to the body of literature which seeks to investigate the underlying neurobiology of non-motoric symptoms in HD.

Disclosures: S.R. Moldenhauer: None. **S. Lipkin:** None. **A.L. Southwell:** None. **B. Fry:** None.

Poster

PSTR331: Huntington’s Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.14/Web Only

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Canadian Institutes of Health Research Project Grant GR030433
Brain Canada Canadian Optogenetics Vectrology Foundry

Title: Aberrant excitation and inhibition in the zQ175 Huntington Disease mouse model: role of NMDA receptor in the spread of sensory cortex activity

Authors: *Y. WANG, M. D. SEPERS, D. RAMANDI, A. AGUASON, W. REES-JONES, J. P. MACKAY, L. A. RAYMOND;
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The neurodegenerative disorder, Huntington Disease (HD), is caused by CAG trinucleotide repeat expansions >35 in the Huntingtin (*HTT*) gene, encoding huntingtin (Htt). Previously, our group reported enhanced spread of layer II/III cortical responses to sensory stimulation in HD mice models at the motor-manifest stage. In contrast, our new data (unpublished) shows no increased spread of sensory stimulation-induced cortical responses in premanifest HD mice. Here, we investigated cortical excitation and inhibition in zQ175 knock-in HD-model mice expressing GCaMP6s compared to their wild-type littermates, using *ex vivo* (acute brain slice) calcium imaging and electrophysiology to explore mechanisms of cortical sensory spread. The excitatory-inhibitory (E-I) balance of evoked synaptic currents of layer II/III cortical pyramidal neurons (CPNs) from zQ175 mice increased with age from the premanifest (3-4 months) to manifest stage (8-9 months). Consistent with the idea of cortical network hyper-excitability, more zQ175 CPNs than WT CPNs showed evoked large-amplitude excitatory discharges at both the premanifest and manifest stages. Ifenprodil treatment (which selectively inhibits GluN2B-containing NMDARs), decreased the area and peak of these discharges and the spread of evoked cortical activity of excitatory neurons in *ex vivo* slices, while near complete elimination was achieved with subsequent APV treatment (NMDAR inhibitor). Preliminary data shows more pronounced ifenprodil-mediated reduction in zQ175 mice. Together these data suggest increased 2B-NMDAR expression - thought to trigger cell stress/death pathways - in the sensory cortex of zQ175 mice. Since the frequency of spontaneous inhibitory post-synaptic currents recorded from sensory CPNs also decreased with age in zQ175 mice, and the intrinsic excitability of fast-spiking interneurons was reduced in manifest zQ175 compared to age-matched WT mice, future investigations will examine the pharmacological effect of ifenprodil and APV treatment on the spread of evoked cortical activity of PV interneurons. Aberrant NMDAR-mediated large-amplitude discharges and reduced inhibitory drive may therefore underlie E-I imbalances that result in circuit changes and synaptic dysfunction ultimately contributing to enhanced sensory spread in HD.

Disclosures: Y. Wang: None. **M.D. Sepers:** None. **D. Ramandi:** None. **A. Aguason:** None. **W. Rees-Jones:** None. **J.P. Mackay:** None. **L.A. Raymond:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.15/C51

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NSFC of China

Title: Gene Therapy for Huntington's Disease using large animal models @font-face {font-family:SimSun; panose-1:2 1 6 0 3 1 1 1 1 1; mso-font-alt:宋体; mso-font-charset:134; mso-generic-font-family:auto; mso-font-pitch:variable; mso-font-signature:3 680460288 22 0 262145 0;}@font-face {font-family:"Cambria Math"; panose-1:2 4 5 3 5 4 6 3 2 4; mso-font-charset:0; mso-generic-font-family:roman; mso-font-pitch:variable; mso-font-signature:3 0 0 0 1 0;}@font-face {font-family:"\@SimSun"; panose-1:2 1 6 0 3 1 1 1 1 1; mso-font-charset:134; mso-generic-font-family:auto; mso-font-pitch:variable; mso-font-signature:3 680460288 22 0 262145 0;}p.MsoNormal, li.MsoNormal, div.MsoNormal {mso-style-update:auto; mso-style-unhide:no; mso-style-qformat:yes; mso-style-parent:""; margin-top:0cm; margin-right:0cm; margin-bottom:8.0pt; margin-left:0cm; text-align:justify; text-justify:inter-ideograph; line-height:150%; mso-pagination:widow-orphan; font-size:12.0pt; mso-bidi-font-size:11.0pt; font-family:"Times New Roman",serif; mso-fareast-font-family:SimSun; mso-ansi-language:EN-US;}.MsoChpDefault {mso-style-type:export-only; mso-default-props:yes; font-fami

Authors: *S.-H. LI;
GHM CNS regeneration, Jinan Univ., Guangzhou, China

Abstract: Huntington's disease (HD) is caused by the expansion of CAG repeat sequences in the first exon of the huntingtin (HTT) gene. Mutant huntingtin (mHTT) with expanded PolyQ preferentially causes striatal neurodegeneration. Currently, there is no effective cure for HD. The HD knock-in pig model, which mimics striatal neurodegeneration seen in HD patients, provides a valuable platform for studying HD pathogenesis and developing therapeutic strategies. Our research revealed that aberrant spliced HTT exon1 is also present in the brains of HD pigs, but it is expressed at a much lower level than the normally spliced HTT exon products, indicating that mutant HTT exon 1 is a major toxic product in HD. Consistently, disrupting or repairing mutant HTT exon 1 in HD knock-in pigs using CRISPR/Cas9 could alleviate neuropathology and movement abnormalities. However, non-allele-specific targeting with CRISPR/Cas9 may inadvertently affect the wild-type HTT, potentially impacting its normal function. Considering that HTT's function is age-dependent, we investigated whether CRISPR/Cas9-mediated HTT depletion in the adult monkey brains posed harm to neuronal cells. Our findings demonstrated no significant effects of HTT deletion on neuronal and glial cells in the brain striatum of adult cynomolgus monkeys for up to two months. Further long-term studies are ongoing to explore whether simple disrupting exon 1 of HTT in the striatum of adult primates could serve as a viable intervention strategy for HD.**Key word**:Huntington's disease, Large animal models, Gene Therapy, Polyglutamine.

Disclosures: S. Li: None.

Poster

PSTR331: Huntington’s Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.16/C52

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant R01NS125742
Simons Foundation: NC-SURFiN-00003289

Title: Utilizing the novel HD-BXD mouse panel to investigate cognitive performance in Huntington's disease

Authors: *H. C. LYONS[1], L. J. BENOVICH[1], G. KAUL[2,3], A. VANLIANUK[1], A. D. EBAN-ROTHSCHILD[2], S. M. BOAS[1], C. C. KACZOROWSKI[1];
[1]Neurol., Univ. of Michigan, Ann Arbor, MI; [2]Psychology, Univ. of Michigan, Ann Arbor, MI; [3]Computer Science & Engineering, University of Michigan, Ann Arbor, MI

Abstract: Huntington's disease (HD) is a dominantly-inherited neurodegenerative disorder caused by a trinucleotide CAG repeat expansion in the huntingtin gene (HTT). HD diagnosis typically follows motor symptom onset; however, cognitive dysfunction also severely impacts patient quality of life, and is often overlooked when it precedes motor onset. Previous studies report substantial variability in clinical presentation of HD non-motor features, even between individuals with comparable CAG repeat length. We hypothesize that this variation could be due to individual genetic differences beyond HTT expansion; our goal is to identify genetic factors which determine the severity of cognitive decline in the context of HD. To investigate the role of genetic background on HD cognitive decline, we generated a novel mouse panel to evaluate differential effects of HTT expansion across diverse genetic backgrounds. This mouse panel was created by crossing the HttQ111 (Q111) knock-in HD model to several recombinant inbred BXD strains (HD-BXD Mouse Panel). Results presented here are part of a larger phenotypic characterization study to assess motor, cognitive, and neuropsychiatric HD-relevant traits at multiple age points in female Q111 carriers and their non-transgenic (Ntg) littermates. Cognitive performance is currently being evaluated across the HD-BXD mouse panel in young (3 months) and aged (12 months) females using a two-day passive avoidance paradigm. This is a long-term memory task where on Day 1, animals are given a mild foot shock in the dark side of a light-dark chamber. On Day 2, the animal's latency-to-cross to the dark chamber and total time spent on each side are recorded. Better memory is indicated by a longer latency-to-cross and less time spent in the dark chamber on Day 2. Video analysis was performed using Detect Any Mouse Model (DAMM), a deep learning module designed for mouse detection in complex environments. We will next evaluate the contribution of genetic background variation to cognitive performance in the HD-BXD panel through the calculation of broad sense heritability and quantitative trait loci mapping. Genetic modifiers identified in this study will inform novel therapeutic strategies for cognitive decline in HD.

Disclosures: H.C. Lyons: None. **L.J. Benovich:** None. **G. Kaul:** None. **A. Vanlianuk:** None. **A.D. Eban-Rothschild:** None. **S.M. Boas:** None. **C.C. Kaczorowski:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.17/C53

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: R01NS125742
NC-SURFiN-00003289

Title: Utilizing the novel Q111-BXD mouse panel to explore the neuropsychiatric traits of Huntington's Disease

Authors: *L. J. BENOVICH, H. C. LYONS, A. VANLIANUK, S. SINGH, S. M. BOAS, C. C. KACZOROWSKI;
Dept. of Neurol., Univ. of Michigan, Ann Arbor, MI

Abstract: Huntington’s disease (HD) is a dominantly-inherited disorder caused by CAG repeat expansion in the huntingtin (*HTT*) gene. HD is neurodegenerative in nature, and symptoms comprise motor, cognitive, and neuropsychiatric features. HD neuropsychiatric symptoms, such as depression and anxiety, typically appear before hallmark motor symptoms; they are also reportedly the most debilitating disease features, contributing most to decline in quality of life in HD patients. Generally, individuals harboring longer CAG repeats exhibit more severe and earlier onset of symptoms; however, there is substantial variation in these clinical phenotypes even among patients with identical CAG repeat lengths. This variation may be explained by additional genes or gene interactions which modify HD symptom severity. Furthermore, unlike HD motor symptoms, CAG repeat lengths are even less predictive of the severity and onset of neuropsychiatric traits, and the biological mechanisms underlying neuropsychiatric traits are poorly understood. Identifying potential genetic drivers and modifiers of these symptoms could illuminate relevant pathways for novel therapeutic strategies. We have developed a novel HD mouse panel on a genetically diverse background (HD-BXD) in order to investigate the heritability of HD phenotypes and identify genetic modifiers of HD-relevant traits. The HD-BXD mouse panel was generated by crossing the Q111 knock-in HD model to several genetically-segregated BXD strains. Variation in genetic background between HD-BXD strains allows for quantitative trait loci (QTL) mapping to identify regions of the genome which contribute to HD-relevant neuropsychiatric phenotypes. To assess depressive-like behavior, we utilized the tail suspension test, where mice are suspended by their tail. Increased depressive-like behavior is indicated by increased time spent immobile. Additionally, we evaluated anxiety-like activity from exploratory behavior in open field. Briefly, mice are placed in an illuminated arena for 10 minutes where their movement is video-recorded and analyzed using DeepLabCut. Tail suspension and open field assays were run in 3- and 12-month female Q111 carriers and non-transgenic littermate controls. QTL mapping of each trait was used to identify potential genetic modifiers of depressive- and anxiety-like phenotypes in this panel. Genetic modifiers identified in this study will be cross-referenced with human HD data to inform novel therapeutic strategies for mood disturbances in HD.

Disclosures: L.J. Benovich: None. **H.C. Lyons:** None. **A. Vanlianuk:** None. **S. Singh:** None. **S.M. Boas:** None. **C.C. Kaczorowski:** None.

Poster

PSTR331: Huntington’s Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.18/C54

Topic: C.04. Movement Disorders other than Parkinson"s Disease

Support: NIH Grant R01NS125742
Simon's Foundation NC-SURFiN-00003289

Title: Utilizing the novel HD-BXD mouse panel to identify genetic modifiers of Huntington's disease-relevant traits

Authors: *S. M. BOAS[1], A. VANLIANUK[2], L. BENOVICH[1], H. C. LYONS[3], C. C. KACZOROWSKI[4];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Neurol., Univ. of Michigan, Ann Arbor, MI; [3]Dept. of Neurol., Univ. of Michigan, Ann Arbor, MI; [4]Neurol., The Univ. of Michigan, Ann Arbor, MI

Abstract: Huntington’s disease (HD) is a dominantly-inherited neurodegenerative disease caused by pathogenic CAG repeat expansion within the huntingtin (*HTT*) gene. While diagnosis is typically confirmed by genetic testing following the onset of involuntary movement episodes, comorbid psychiatric and cognitive symptoms are also major contributors to loss of patient autonomy and caregiver burden. CAG repeat length is generally predictive of disease severity, with earlier onset and worsened symptomology associated with longer repeats; however, substantial variation exists, even between individuals with identical repeat lengths. This discrepancy suggests that ‘resilient’ HD carriers may harbor additional genetic variants which delay/attenuate HD progression. To model variation observed in human disease, we utilized a Q111 knock-in HD mouse model crossed to a panel of genetically-segregated (BXD) backgrounds (HD-BXD Mouse Panel). We are currently testing female Q111 carriers and non-transgenic (Ntg) littermates on a battery of motor (rotarod, wire-hang), cognitive (passive avoidance), and mood (tail suspension, open field) assays to assess variation and heritability of HD-relevant traits across BXD strains and in various age cohorts. For each assay, we will determine if inherited Q111 CAG length predicts performance on HD-relevant behavioral tasks. Additionally, we will perform quantitative trait loci (QTL) mapping in order to identify genetic factors that modify motor, cognitive, and/or neuropsychiatric traits. While behavioral assessment is ongoing, preliminary data from seven BXD strains showed that CAG repeat length is negatively correlated with Q111-BXD performance on accelerating rotarod and wire-hang at 6-months of age. Overall, these data demonstrate our panel as a promising translational model of genetic variation in HD. By leveraging the genetic mapping power of the BXD panel, we will identify putative genetic modifiers to illuminate new and desperately needed therapeutic targets for the clinical population.

Disclosures: S.M. Boas: None. **A. Vanlianuk:** None. **L. Benovich:** None. **H.C. Lyons:** None. **C.C. Kaczorowski:** None.

Poster

PSTR331: Huntington’s Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.19/C55

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: R01NS125742

Title: Motor phenotyping at 3 and 12 months of age in genetically diverse mouse model of Huntington's disease

Authors: *A. VANLIANUK[1], S. BOAS[2], L. J. BENOVICH[3], H. C. LYONS[3], C. C. KACZOROWSKI[3];
[1]Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [2]CDIB, Univ. of Alabama Birmingham, Birmingham, AL; [3]Neurol., Univ. of Michigan, Ann Arbor, MI

Abstract: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by abnormal CAG repeat expansion in the huntingtin (HTT) gene. In HD, motor symptoms serve as the hallmark diagnostic criterion. While previous studies have shown that CAG repeat length is generally predictive of age of motor symptom onset and severity, substantial phenotypic variation is observed between patients, even those with identical CAG repeat lengths. This variation suggests that beyond inherited CAG length, there are genetic modifiers which differentially influence HD motor symptoms. However, HTT expansion (mHTT) carriers are exceedingly rare, making animal models a more appealing strategy for HD genetic modifier screens. Therefore, we have generated a genetically diverse HD mouse model by crossing the Q111 knock-in HD mouse to several strains from the BXD mouse panel (HD-BXD). Genetic variation across this panel allows for quantitative trait loci mapping. In this panel, motor behavior of female Q111 carriers and non-transgenic (Ntg) littermates was assessed using an accelerating rotarod and open field assays. At three months of age, we found that motor performance on rotarod and open field is highly heritable among HD-BXD strains. This demonstrates the contribution of genetic background to the variation in motor performance. Furthermore, even at this early age, we found a candidate of susceptible strain when comparing between genotype within each BXD strain. Assessment of motor performance in the 12-month cohort is ongoing to find resilient and susceptible strains. QTL mapping of motor traits in this mouse panel will allow us to identify potential genetic modifiers of HD motor dysfunction and inform disease-modifying therapeutic strategies.

Disclosures: A. Vanlianuk: None. **S. Boas:** None. **L.J. Benovich:** None. **H.C. Lyons:** None. **C.C. Kaczorowski:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.20/C56

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI (to Gerardo Morfini)
NINDS R21NS096642 (to Gerardo Morfini)

Title: Aberrant activation of the JNK pathway by mutant huntingtin is mediated by discrete SH3-binding motifs in the proline-rich domain.

Authors: M. KANG[1,2], S. KALL[3], Y. SONG[5,2], M. A. POULADI[6], A. LAVIE[4], S. T. BRADY[7,2], ***G. MORFINI**[3,2];
[1]Anat. and Cell Biol., Univ. of Illinois At Chicago, Chicago, IL; [2]Marine Biol. Lab., Woods Hole, MA; [4]Dept. of Biochem. and Mol. Genet., [3]Univ. of Illinois at Chicago, Chicago, IL; [5]Neurol., Harvard Med. School/Mass Gen. Hosp., Charlestown, MA; [6]Med. Genet., Univ. of British Columbia, Vancouver, BC, Canada; [7]Anat. and Cell Biol., UIC, Chicago, IL

Abstract: Mutations that promote aberrant expansion of a polyglutamine tract (polyQ) in the protein huntingtin (HTT) are the primary cause of Huntington's disease (HD), a devastating human neurodegenerative disorder featuring devastating cognitive and motor symptoms. Toxic effects of mHTT have been mapped to a protein fragment encoded by exon 1 of the mutant HTT gene (mHTT exon 1), which encompasses a short amino-terminal domain, a polyglutamine tract (polyQ), and a proline-rich domain (PRD). Compelling evidence established that polyQ expansion confers upon mHTT a toxic gain-of-function that affects numerous cellular activities including gene transcription, mitochondrial function, kinase signaling, endocytosis, and axonal transport, among others. A major open question in the field of HD research is how does mHTT promote so many seemingly unrelated impairments.A potential mechanism contributing to mHTT toxicity emerges from consideration of two well-established findings: 1) polyQ tract expansion promotes mHTT misfolding and aberrant exposure of the PRD; 2) the PRD reportedly interacts with various ligands, including several SH3 domain-containing proteins, involved in a wide variety of cellular activities. Collectively, these findings suggest that toxic effects elicited by mHTT might involve aberrant PRD interactions with specific protein ligands.Here, we report the mapping of two novel SH3-binding motifs in the PRD of HTT, a finding that provided a unique opportunity to advance our understanding of this domain's contribution to mHTT toxicity. Experiments using a unique ex vivo preparation show the newly identified motifs are necessary for mHTT to promote abnormal activation of axonal JNK kinases and impairments in axonal transport associated with their activation. Consistent with these findings, our studies revealed a specific MAP kinase upstream of JNK kinases as a ligand for one of the specific SH3 binding motifs identified in our studies.Collectively, our data support an innovative mechanistic model where abnormal exposure of the PRD in mHTT would promote aberrant interactions of this domain with specific SH3 domain-containing proteins, including a MAPK kinase upstream of JNK kinases

Disclosures: M. Kang: None. **S. Kall:** None. **Y. Song:** None. **M.A. Pouladi:** None. **A. Lavie:** None. **S.T. Brady:** None. **G. Morfini:** None.

Poster

PSTR331: Huntington's Disease: Molecular and Cellular Mechanisms in Mouse Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR331.21/C57

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI
Dake Family Fund

Title: Unveiling early oligodendrocyte lineage dysregulation in a neurodegenerative disease mouse model

Authors: *A. BOUDI[1], E. SAPP[1], K. SHING[1], T. PETROZZIELLO[2], G. SADRI-VAKILI[2], M. DIFIGLIA[1], X. LI[1];
[1]Neurol., Massachusetts Gen. Hosp. - Harvard Med. Sch., Boston, MA; [2]Neurol., Sean M. Healey & AMG Ctr. for ALS at Mass Gen., MassGeneral Brigham, Boston, MA

Abstract: Huntington's disease (HD) is a devastating inherited neurodegenerative disorder marked by severe grey matter atrophy, predominantly in the caudate, putamen and cerebral cortex. Notably, early and significant deteriorations in white matter regions, composed mainly of myelinated axons and glial cells, are observed in HD patients. The underlying mechanistic events occurring remain poorly understood. Only recently, single-cell RNA sequencing data from post-mortem patients and an HD mouse model reported impaired maturation of oligodendrocytes, cells responsible for myelin generation.
In this study, we used HDQ140/Q140 mouse, a model that biologically replicates the disease in humans- to investigate the mechanisms of white matter decay in HD. Among the myelin-related proteins examined, the first to display reduced levels in HD condition is the Myelin-Associated Glycoprotein (MAG), which is located at the interface between oligodendrocytes and neurons. Histological analysis of brain tissue revealed that MAG reactivity was broadly reduced, particularly in bundle areas, but importantly, also accumulated in a subset of cells. We identified these cells as newly generated oligodendrocytes. Our hypothesis posits that defective MAG targeting is a critical event in white matter pathology in HD. Ongoing studies aim to characterize structures where MAG is accumulated. The approaches applied include cryo-immuno gold electron microscopy in brain slices, and live-cell imaging of MAG trafficking in *in vitro* differentiated oligodendrocytes. Furthermore, we will explore whether and how neuronal signaling impacts MAG targeting.
Our findings underscore the early defects in oligodendrocyte maturation and offer insights into white matter pathology in other neurodegenerative pathologies with leukodystrophy components, such as Alzheimer's disease.

Disclosures: A. Boudi: None. **E. Sapp:** None. **K. Shing:** None. **T. Petrozziello:** None. **G. Sadri-Vakili:** None. **M. Difiglia:** None. **X. Li:** None.

Poster

PSTR332: ALS: *Drosophila* and Non-iPSC Cell Culture Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR332.01/Web Only

Topic: C.06. Neuromuscular Diseases

Support: ICMR Neuro/213/2020-NCD-1
EMSTAR 2023
Intramural IISER Pune fellowship
BDSC Indiana

Title: Differential Roles of Ceramide in the brain and it's implications in a Drosophila model of Amyotrophic Lateral Sclerosis

Authors: *L. GARG[1], K. CHAPLOT[2], S. TENDULKAR[3], S. KAMAT[4], G. RATNAPARKHI[4]; [1]Biol., Indian Inst. of Sci. Educ. and Research, Pune, India, Pune, India; [2]Ophthalmology and Physiol., Univ. of California San Francisco, San Francisco, CA; [3]Developmental Biol., Washington Univ. in St. Louis, Sch. of Med., St. Louis, MO; [4]Biol., Indian Inst. of Sci. Educ. and Res., Pune, India

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by loss of motor neurons leading to gradual paralysis and death of the patient within 2-5 years post diagnosis. 10% of patients show familial inheritance, with 90% of the disease being sporadic. More than 30 independent genetic loci have been associated with ALS. *VAMP Associated Protein B* [*VAPB/ALS8*] is the 8th locus identified, where a point mutation from Proline to Serine at 56th position cause ALS. A similar point mutation at the 58th position in VAPB is used to model ALS in *Drosophila*. VAPB is a Type-II integral ER membrane protein with three defined domains namely Major Sperm Protein (MSP), Coiled-Coil Domain (CCD) and Transmembrane Domain (TMD). A number of lipid transfer proteins are known to interact with the MSP domain via their FFAT motif. Ceramide Transfer (*CERT*) is one such interactor of *VAPB* whose main function is to transfer ceramide from ER to Golgi in the cell for sphingomyelin synthesis. *CERT*$^{\Delta}$ flies show worsening motor ability and reduced lifespan because of low ceramide and sphingomyelin levels (Rao *et al.*, 2007). Using genetic tools of flies, we modulated *CERT* levels in both neurons and glia of *Drosophila*. Surprisingly, we observe differential role of *CERT* in neurons and glia. Loss of *CERT* in glia deteriorates motor activity of wild-type flies. However, in neurons loss of *CERT* does not affect flies behavior at all. Interestingly, overexpressing *CERT* in glia leads to partial rescue of *CERT*$^{\Delta}$ defects. Using LC-MS lipid profiling, we have found that ceramide and their derivatives are upregulated in the *VAP*^{P58S} brain. CERT modulation in glia worsens the motor phenotype of ALS flies. So, we targeted *CERT* and ceramide synthesis genes in neurons of the mutant flies and loss of their activity led to partial rescue of the motor ability of ALS8 flies. Mechanistically, ROS is a known player in both *CERT*$^{\Delta}$ and *VAP*^{P58S} flies (Rao *et al.*, 2007; Chaplot *et al.*, 2019) , and we believe a cross-talk occurs between ROS and ceramide levels in the brain, which affects motor behavior of *Drosophila*.

Disclosures: L. garg: None. **K. Chaplot:** None. **S. Tendulkar:** None. **S. Kamat:** None. **G. Ratnaparkhi:** None.

Poster

PSTR332: ALS: *Drosophila* and Non-iPSC Cell Culture Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR332.02/C58

Topic: C.06. Neuromuscular Diseases

Title: Muscle-restricted expression of C9orf72 expanded RNA repeats induces toxicity in Drosophila melanogaster

Authors: *J. PARAMESWARAN[1], Z. WANG[2], D. PANT[3], J. JIANG[4];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that impacts both upper and lower motor neurons of the central nervous system. It is primarily characterized by the gradual weakening of muscles, ultimately leading to respiratory failure. Unfortunately, a cure for this disease remains elusive to date. Expanded GGGGCC hexanucleotide repeats in the C9orf72 gene have been identified as the most prevalent genetic cause of ALS. These expanded repeats are transcribed bidirectionally to form both sense (G4C2) and antisense (C4G2) RNA species, which subsequently produce five unique dipeptide repeat proteins: GA, GR, GP, PA, and PR. Numerous studies support the concept that the gain of toxicity from sense repeat expanded RNAs plays a central role in the pathogenesis of ALS/FTD. Given that most of these studies are limited to neurons and the recent unsuccessful translation of preclinical findings to humans, it is important to thoroughly investigate the role of repeat RNA in other affected tissues, including muscles. Nonetheless, emerging evidence supports a more active involvement of skeletal muscle in ALS progression, indicating its potential as a therapeutic target. Interestingly, most previous studies focused on atypical forms of ALS mutations such as SOD1, FUS, and the contribution of muscles in the context of C9orf72 HRE is not well explored. Our data suggest that both sense and antisense RNA themselves can induce toxicity in Drosophila when expressed ectopically in muscles. Moreover, we also observed neuromuscular junction (NMJ) defects in repeat-expressing flies compared to controls. These results imply that the presence of C9orf72 expanded RNA repeats in muscles plays an essential role in ALS disease pathogenesis, and the underlying molecular mechanisms need to be explored in future research.

Disclosures: J. Parameswaran: None. **Z. Wang:** None. **D. Pant:** None. **J. Jiang:** None.

Poster

PSTR332: ALS: *Drosophila* and Non-iPSC Cell Culture Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR332.03/C59

Topic: C.06. Neuromuscular Diseases

Support: NIA RF1AG076493
NIA R01AG078788)

Title: Trigger Warning: Do psychological stressors trigger neurodegeneration in a Drosophila TDP-43 model?

Authors: N. H. MEKAWY[1,2], S. MURTHYGOWDA[3], *J. DUBNAU[4,2];
[1]Neurobio. and Behavior, [2]Program in Neurosci., Stony Brook Univ., Stony Brook, NY;
[3]Anesthesiol., [4]Dept. of Neurobio. and Behavior, Dept. of Anesthesiol., Stony Brook Sch. of Med., Stony Brook, NY

Abstract: Trigger warning: Do psychological stressors trigger neurodegeneration in a Drosophila TDP-43 model?
Narmin Mekawy[1,2] Swetha Gowda[3] and Josh Dubnau[1,2,3]
Affiliations. 1-**Program in Neuroscience, Stony Brook University**2-**Dept of Neurobiology and Behavior, Stony Brook University**3-**Dept of Anesthesiology, Stony Brook Medicine**
Abstract:Aging is a major risk factor of onset of neurodegeneration; Other risk factors include post-traumatic stress disorder, emotional stress, obesity, and environmental toxins. From epidemiological studies, however, it is not possible to determine to what extent biological aging, cumulative effects of lifelong stress, or early life stresses act to trigger onset of neurodegeneration. The mechanisms by which psychological stress may drive disease are also not known. Genetically inducing TDP-43 pathology in animal models is sufficient to trigger progression of neurodegenerative phenotypes. For example, in Drosophila, inducing TDP-43 over-expression in glial cells can trigger spread of neurodegeneration to other glia and to neurons. This is associated with loss of nuclear TDP-43, accumulation of cytoplasmic inclusions, expression of retrotransposons and endogenous retroviruses, and appearance of DNA damage. The major goal of this project is to identify behaviorally stressful environmental percepts that are sufficient to either trigger spontaneous neurodegenerative effects, or to exacerbate the effects of genetic models of neurodegeneration. This would provide the first animal model to investigate the mechanisms of the upstream triggers of neurodegeneration. This project is at an early stage, and we present ideas and preliminary findings. To investigate the upstream triggers of neurodegeneration, we are testing the effects of “psychological stressors" by providing stressful perceptual experiences to flies that are genetically sensitized towards TDP-43 neurodegeneration. We are testing the impacts of these manipulations on lifespan, TDP-43 protein pathology and other markers of neurodegeneration. In this poster, we show preliminary data for 4 experimental strategies to expose flies to ‘psychological’ stressors: perception of predation risk, frustration of mating potential, restraint stress and social isolation.

Disclosures: N.H. Mekawy: None. **S. Murthygowda:** None. **J. Dubnau:** None.

Poster

PSTR332: ALS: *Drosophila* and Non-iPSC Cell Culture Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR332.04/C60

Topic: C.06. Neuromuscular Diseases

Support: NIA R01 AG068043
NINDS T32 NS091018

Title: Dysregulated Wnt signaling contributes to C9-ALS/FTD pathogenesis in Drosophila models

Authors: *M. D. EWING[1], T. E. LLOYD[2];
[1]Neurosci., Johns Hopkins, Baltimore, MD; [2]Neurol. and Neurosci., Baylor Col. of Med., Houston, TX

Abstract: The most common genetic cause of both amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) is a G_4C_2 repeat expansion in the *C9orf72* gene (C9-ALS/FTD). Prior studies in mouse models, *in vitro*, and in postmortem tissue have found evidence of Wnt signaling dysregulation in both genetic and sporadic forms of ALS. However, the ramifications of these changes in the Wnt pathway and their effect on neuronal health are not known. In *Drosophila* models of C9-ALS/FTD, we found upregulation of Wingless (Wg), the primary Wnt ortholog, in the adult brain. This Wg upregulation increased levels of Armadillo/β-catenin, indicative of downstream activation of the canonical Wnt signaling pathway. Wg upregulation was also observed in fly FUS and TDP-43 ALS models, but not in a *Drosophila* tauopathy model. This suggests that aberrant Wnt pathway activation may be a specific feature of TDP-43 proteinopathies, but not neurodegeneration with tau pathology. To understand the effect of Wnt signaling upregulation on the mature nervous system, we used Elav- or Repo- GeneSwitch to conditionally upregulate Wg in adult neurons or glia. Wg overexpression in either cell type resulted in impaired survival and increased neuronal cell death. Additionally, neuronal Wg overexpression was sufficient to cause mislocalization of several nucleoporins, similar to our observations in C9-ALS/FTD models. To determine whether Wg upregulation contributes to C9-ALS/FTD pathogenesis, we knocked down Wg in fly C9-ALS/FTD models. Knockdown of Wg or the Wg regulator Dally-like protein (Dlp) extended lifespan and reduced neuronal apoptosis. Together, this shows that aberrant Wg signaling upregulation may be a detrimental event that contributes to C9-ALS/FTD pathogenesis.

Disclosures: M.D. Ewing: None. **T.E. Lloyd:** None.

Poster

PSTR332: ALS: *Drosophila* and Non-iPSC Cell Culture Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR332.05/C61

Topic: C.06. Neuromuscular Diseases

Support: NIH GRANT NS111000

Title: Modeling a familiar form of optineurin-associated ALS in fruit flies

Authors: *S. HAQUE, R. INSOLERA;
Wayne State Univ., Detroit, MI

Abstract: Amyotrophic Lateral Sclerosis (ALS), often referred to as Lou Gehrig's disease, is a progressive neurodegenerative disorder characterized by the degeneration of motor neurons in the brain and spinal cord. ALS can manifest as either sporadic, with no known genetic link, or familial, with a clear genetic component. In familial cases, specific mutations have been identified as causative factors, shedding light on the potential underlying molecular mechanisms of the disease. One such mutation occurs in the Optineurin (OPTN) gene. Optineurin is a multifunctional protein involved in various cellular processes, including autophagy, vesicle trafficking, and regulation of inflammation. Our study aims to model a form of OPTN-associated ALS in Drosophila melanogaster, elucidating the mechanisms by which OPTN mutations contribute to disease pathology. Our lab has recently discovered the fruit fly homolog of OPTN, dOPTN (also known as Kenny). When aligned with human OPTN protein, a mutated amino acid associated with a familial form of ALS is conserved in the fruit fly protein: E478 in human is homologous to E283 in flies. We find that expression of the ALS-associated equivalent mutant of dOPTN (E283G) in fly neurons results in severe aggregation of the protein. My project seeks to examine the physiological effects of expressing this mutant protein in fly neurons by examining the age-dependent effects of mutant OPTN protein aggregation on fly locomotor activity. Through this investigation, we seek to uncover the interplay between protein aggregation and neuronal dysfunction in order to provide insights into the underlying molecular mechanisms of ALS pathology.

Disclosures: S. Haque: None. **R. Insolera:** None.

Poster

PSTR332: ALS: *Drosophila* and Non-iPSC Cell Culture Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR332.06/C62

Topic: C.06. Neuromuscular Diseases

Title: Impaired proteasome activity and autophagy-lysosome pathway exacerbates motor neuron loss and TDP43 proteinopathy in in vitro models of amyotrophic lateral sclerosis.

Authors: *A. HENRIQUES, N. CALLIZOT;
Neuro-Sys, Inc., GARDANNE, France

Abstract: Amyotrophic lateral sclerosis (ALS) is an adult motor neuron disease characterized by the loss of upper and lower motor neurons (MNs) and muscle denervation. Toxic gain-of-function mutations of superoxide dismutase type-1 (SOD1), an antioxidant enzyme whose activity is preserved in most mutant forms, have been linked to familial cases of ALS. Mutants SOD1 transgenic animals and cellular models are useful tools to study the disease.

Neurodegeneration of spinal MNs and loss of neuromuscular junctions in ALS are caused by complex and multifactorial pathological events, including the accumulation of misfolded proteins, such as TDP43 or SOD1. Proteinopathy in ALS is progressive over time and across CNS areas. Misfolded proteins can be degraded by lysosomes via autophagy lysosomal pathway (ALP) and by the ubiquitin-proteasome system (UPS). In vitro models of ALS, based on spinal MNs, are used to investigate the pathophysiology of the disease. Here, we investigated the activation of ALP and UPS in in vitro models of ALS and determined their contribution to reducing protein aggregation in spinal MNs. Primary spinal MNs from SOD1 G93A Tg or wild type (WT) rats were cultured for 14 days and injured with glutamate (5 µM, 20 minutes). Pharmacological agents targeting ALP (i.e. bafilomycin A) and UPS (i.g. MG132) were applied to the cultures. Immunostaining and automated image analysis were applied to investigate neuronal survival, integrity of the neurite network, abnormal cytoplasmic accumulation of TDP43 and markers of ALP and UPS pathways, 24 hours after glutamate stress. Our results showed clear accumulation of lysosomes and autophagosomes, markers of ALP, and a reduction in proteasome activity in the culture of spinal SOD1 G93A Tg MNs. When exposed to glutamate-induced injury, there was a clear loss of spinal MNs and abnormal cytoplasmic accumulation of phosphorylated TDP43, with the effects being more pronounced in SOD1 Tg MNs when compared to WT cultures. Inhibition of ALP and UPS drastically exacerbated TDP43 proteinopathy and neurodegeneration, while pharmacological activators of protein clearance pathway supported neuronal survival. Altogether, these findings demonstrate that protein clearance pathways are activated in basal condition in SOD1 Tg in vitro model of ALS and that impairments in ALP or UPS leads to severe neuronal loss after exposure to glutamate.

Disclosures: A. Henriques: A. Employment/Salary (full or part-time):; Neuro-Sys. **N. Callizot:** A. Employment/Salary (full or part-time):; Neuro-Sys.

Poster

PSTR332: ALS: *Drosophila* and Non-iPSC Cell Culture Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR332.07/C63

Topic: E.09. Motor Neurons and Muscle

Support: W81XWH-22-1-0218

Title: Effects of the G-quadruplex binder, protoporphyrin IX, and its precursor, 5-aminolevulinic acid, on TDP-43 aggregation in NSC34 motor neuronal cells

Authors: *M. E. SPAETH HERDA[1], E. ELSHALIA[2], D. A. LINSEMAN[3], S. HOROWITZ[4]; [1]Univ. of Denver, Westminster, CO; [2]Chem. & Biochem., Univ. of Denver, Denver, CO; [3]Biol., Univ. of Denver, Denver, CO; [4]Univ. of Denver, Denver, CO

Abstract: SFN 2024 Abstract Effects of the G-quadruplex binder, protoporphyrin IX, and its precursor, 5-aminolevulinic acid, on TDP-43 aggregation in NSC34 motor neuronal cells

McKenna Spaeth Herda, Eman Elshalia, Daniel A. Linseman, Scott Horowitz
Departments of Biology and Chemistry/Biochemistry, University of Denver, Denver, CO, USA
Pathological protein aggregation is a key feature of amyotrophic lateral sclerosis (ALS), a debilitating neurodegenerative disorder that causes motor neuron death, skeletal muscle atrophy, and eventually death in patients. The variety of pathogenic proteins that drive different forms of ALS through their misfolding and aggregation (e.g., SOD1, FUS, TDP-43) increase the complexity of developing therapeutics to target this disease mechanism. However, TDP-43 aggregation has emerged as the most common pathogenic mechanism in sporadic ALS, as well as some forms of familial ALS. The nucleic acid structure, G-quadruplex, has been implicated in the regulation of pathogenic protein aggregation. Protoporphyrin IX (ppIX) is a metabolic product derived from 5-aminolevulinic acid (5ALA) that has previously been shown to bind G-quadruplexes. We hypothesized that 5ALA or ppIX would prevent the formation of pathological TDP-43 aggregates commonly found in ALS-affected motor neurons. To test this hypothesis, we treated differentiated NSC34 mouse motor neuronal cells overexpressing human wild-type TDP-43 with the oxidative stressor, sodium arsenite, alone or in combination with either 5ALA or ppIX and measured the formation of TDP-43 aggregates and cell viability. Preliminary results suggest that treatment with either 5ALA or ppIX increases viability in TDP-43 overexpressing NSC34s. In addition, fixed cell imaging indicates a decrease in the nuclear export and cytoplasmic aggregation of TDP43 in NSC34s after ppIX treatment. Our results suggest that modulation of TDP43 aggregation by treatment with G-quadruplex binders may be a novel therapeutic avenue to diminish motor neuron death in ALS.

Disclosures: M.E. Spaeth Herda: None. **E. Elshalia:** None. **D.A. Linseman:** None. **S. Horowitz:** None.

Poster

PSTR332: ALS: *Drosophila* and Non-iPSC Cell Culture Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR332.08/C64

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant (DP2GM146322)

Title: Mechanistic insights into mitochondrial oxidative phosphorylation regulation of TDP-43 dynamics in ALS

Authors: *H. E. BALL, A. C. WOODS, Y. C. WONG;
Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease affecting upper and lower motor neurons which currently has no cure. Patients suffer from muscle weakness leading to paralysis and eventual death within 2-4 years of diagnosis. TAR DNA Binding Protein (TDP-43) is an RNA binding protein associated with pathological aggregates in

97% of ALS patients. TDP-43 pathological aggregates accumulate in the cytoplasm and have been proposed to be the result of TDP-43's misregulated shuttling between the nucleus and cytoplasm. However, the mechanisms regulating TDP-43's dynamics over time are still not well understood. In addition, while mitochondrial dysfunction has also been previously linked to ALS pathophysiology, how this pathway modulates TDP-43 shuttling dynamics remains to be further elucidated. Through the utilization of super-resolution live microscopy, we identified a novel mechanistic pathway for mitochondrial regulation of TDP-43. We conducted live imaging to investigate the dynamics of TDP-43 shuttling from the nucleus to the cytoplasm upon modulation of mitochondrial oxidative phosphorylation. Interestingly, we found that this pathway may directly modulate post-translational modifications on TDP-43 to further regulate its shuttling dynamics, with important downstream consequences for additional key cellular proteins. Furthermore, modulating this pathway was sufficient to alter TDP-43's cytoplasmic aggregation, and may inform future therapeutic strategies targeting TDP-43 dynamics and its homeostatic role in both health and disease.

Disclosures: H.E. Ball: None. **A.C. Woods:** None. **Y.C. Wong:** None.

Poster

PSTR332: ALS: *Drosophila* and Non-iPSC Cell Culture Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR332.09/C65

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

Support: NIH Grant R01NS088645
NIH Grant R03AG064266
NIH Grant R01NS094535

Title: Targeting Cytosolic PARylation: A Novel Therapeutic Approach for FUS-Associated Neurodegenerative Diseases

Authors: *M. KODAVATI[1], M. L. HEGDE[2], V. MALOJI RAO[3];
[1]Houston Methodist Res. Inst., Houston,, TX; [2]Houston Methodist, Houston, TX; [3]Houston Methodist Res. Inst., Houston, TX

Abstract: Neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) pose formidable challenges due to their complex etiology, often involving disruptions in pathology of RNA/DNA binding proteins such as FUS and TDP-43. These proteins, when aggregated in the cytosol, form stress granules (SGs), which exacerbate the disease progression. One promising avenue for intervention is the poly-ADP-ribosylase polymerase (PARP)-mediated PARylation mechanism, which plays a pivotal role in this pathological cascade, suggesting therapeutic potential. However, conventional PARP inhibitors, while targeting this mechanism, are encumbered by drawbacks, notably, their impact on DNA repair pathways, which are already compromised in ALS and FTD. To circumvent this

limitation, we propose a novel strategy centered on a cytosol-specific PAR-glycohydrolase isoform, PARG99. This approach aims to mitigate the toxicity caused by FUS aggregation without impeding the crucial nuclear DNA repair mechanisms. Our early investigations in cultured neurons offer promising support for this concept. By focusing on cytosolic targets like PARG99, we aim to develop therapies that effectively address the underlying pathology of ALS and FTD while preserving essential cellular functions like DNA repair. (Research supported by funds from NIH and Houston Methodist Research Institute).

Disclosures: M. Kodavati: None. **M.L. Hegde:** None. **V. Maloji Rao:** None.

Poster

PSTR332: ALS: *Drosophila* and Non-iPSC Cell Culture Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR332.10/C66

Topic: C.06. Neuromuscular Diseases

Title: The Role of Aurora B Kinase in the Development of Neuron Dysfunction in Amyotrophic Lateral Sclerosis

Authors: *S. MARTIN, G. BAUC, L. LOPEZ, M. EISENMENGER, M.-Y. TSAI, S. BRADY; Univ. of Illinois, Chicago, Chicago, IL

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that affects upper and lower motor neurons. While the cause of ALS is unknown, the most common genetic risk factor for ALS is an expansion of a hexanucleotide repeat in the chromosome 9 open reading frame 72 (C9orf72) gene. This repeat expansion leads to the expression and accumulation of 5 different dipeptide repeat proteins; but the extent to which these dipeptide repeats contribute to disease pathogenesis remains a matter of debate. There is evidence that neuronal nuclear dysfunction occurs in many cases of ALS, leading to abnormal size and shape of the nuclei. Our data shows that three of these C9orf72 dipeptide repeats, poly-GP, poly-RP and poly-RG, are neurotoxic when expressed in neuronal cells, and two of them (RP and GP) have both nuclear and cellular pathology whereas GP has only a cellular phenotype. To explore potential mechanisms underlying the development of these pathologies, we focused on a signaling pathway that is critical for regulating nuclear processes. Aurora B kinase is a serine/threonine kinase that localizes to chromosomes and has been reported to play an important role in both mitosis and cytokinesis in differentiating cells, as well as neurite outgrowth in neurons. Based on its predominantly nuclear localization and functions, our hypothesis is that an impairment in Aurora B kinase activation contributes to the development of nuclear pathologies associated with the poly-RP and poly-RG dipeptides. To address this hypothesis, we transfected rat primary cortical neurons from 18-day embryos with expression plasmids containing the C9orf72 dipeptides. We found that there are alterations in Aurora B kinase levels in cells expressing the poly-RP and poly-RG dipeptides, specifically a decrease in cells expressing the poly-RP dipeptide and an increase in cells expressing the poly-RG dipeptide. Treating primary cortical

neurons that were transfected with the dipeptides with a selective Aurora B kinase inhibitor, AZD1152, resulted in a further decrease in neurite length in cells expressing the poly-RP dipeptide and an increase in neurite length in cells expressing the poly-RG dipeptide, suggesting that Aurora B kinase plays a role in axonal processes. Our findings indicate that alterations in Aurora B kinase may be involved in the development of pathological phenotypes in C9orf72-associated ALS, perhaps contributing to an overall mechanism of neurodegeneration.

Disclosures: S. Martin: None. **G. Bauc:** None. **L. Lopez:** None. **M. Eisenmenger:** None. **M. Tsai:** None. **S. Brady:** None.

Poster

PSTR332: ALS: *Drosophila* and Non-iPSC Cell Culture Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR332.11/C67

Topic: C.06. Neuromuscular Diseases

Support: R35GM149211

Title: The FIG4/PIKfyve/VAC14 complex: orchestrating phosphoinositide dynamics in neurodegenerative diseases

Authors: *C. KUTCHUKIAN, M. CASAS PRAT, R. DIXON, E. DICKSON;
Univ. of California Davis, Davis, CA

Abstract: The PIKfyve/FIG4/VAC14 complex is pivotal in modulating the synthesis and turnover of the low-abundance phosphoinositide PtdIns(3,5)P_2 at endosomal membranes. Mutations in the *FIG4* and *VAC14* genes result in reduced cellular levels of PtdIns(3,5)P_2 and are associated with several neurodegenerative disorders, including Amyotrophic Lateral Sclerosis (ALS), Charcot-Marie Tooth type 4J (CMT4J), and Yunis-Varon diseases. However, the precise molecular connections between altered phosphoinositide metabolism and neurodegeneration remain elusive. Through lipidomics, molecular biochemistry, and super-resolution microscopy, we demonstrate that FIG4 and VAC14 loss triggers a dynamic shift of the prevalent monophosphorylated PtdIns(4)P phosphoinositide lipid from Golgi to endomembranes. This shift mirrors changes induced by PIKfyve and VPS34 inhibitors, aimed at reducing PtdIns(3,5)P_2 levels. Mechanistically, we show that the alteration in PtdIns(4)P signaling involves a redistribution of PI(4)P-synthetizing enzyme PI4KIIα, diminishing at Golgi membranes and accumulating at endomembranes. We further reveal a pathway where PIKfyve inhibition reduces mTOR activity, thereby upregulating ULK1-dependent vesicular trafficking of PI4KIIα and the integral membrane protein ATG9A from Golgi to endolysosomes. Increased PtdIns(4)P on endomembranes has a dual impact on neuronal health: it promotes membrane repair and synthesis through enhanced delivery of phosphatidylserine and cholesterol, while also detrimentally affecting mitochondrial morphology and function. Importantly, we show that ULK1 inhibition alleviates these defects. Our findings unveil novel roles for the

FIG4/PIKfyve/VAC14 complex in regulating lysosomal membrane repair mechanisms and controlling mitochondrial function through PtdIns(4)P membrane trafficking.

Disclosures: C. Kutchukian: None. **M. Casas Prat:** None. **R. Dixon:** None. **E. Dickson:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.01/C68

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Sodium phenylbutyrate prevents morphological changes in the hippocampus of rats with CCl_4-induced hepatic encephalopathy

Authors: *D. JUÁREZ SERRANO[1,2], G. FLORES[3], M. MUNOZ ARENAS[2], D. TORRES CIFUENTES[2], I. CESAR ARTEAGA[2], J. MORAN PERALES[3], A. DIAZ[3];
[1]BENEMERITA UNIVERSIDAD AUTONOMA DE PUEBLA, PUEBLA, Mexico; [2]Facultad De Ciencias Químicas, BUAP, Puebla, Mexico; [3]Inst. de Fisiología, BUAP, Puebla, Mexico

Abstract: Hepatic encephalopathy (HE) is the most relevant neuropsychiatric complication in acute and chronic liver failure. Among the inducers of liver damage and fibrosis, toxic reagents are one of the factors that cannot be ignored, and the consequences include toxic effects caused by reactive metabolites, ROS, inflammatory reactions and imbalances between cellular damage and protective responses. Although the hepatotoxicity of carbon tetrachloride (CCl_4) is well known, we have found only a few reports on the effects of CCl_4 on the brain. Sodium phenylbutyrate (PBA) is an orphan drug indicated for urea cycle disorders, although its neuroprotective capacity is currently being explored. The objective of this work is to know the role of PBA on the morphological changes promoted by HE induced by exposure to CCl_4 in a rat model. Twenty-one 3-month-old male Wistar strain rats were used, obtained from the Claude Bernard vivarium of the BUAP. The animals were maintained under standard vivarium conditions. They were randomly divided into 3 experimental groups. Group 1 (CCl_4), Group 2 (PBA) and Group 3 (Control). CCl_4 was prepared in a 1:1 ratio with corn oil, its administration was carried out for 10 weeks, intraperitoneally (i.p.) in the group (CCl_4). The PBA was dissolved in 0.9% NaCl solution, the administered dose was 20 mg/kg of weight, and its administration was carried out for 8 weeks after the induction of HE with CCl_4, i.p. in the (PBA) group. The third group was administered with 0.9% NaCl solution i.p. in the group (Control). After administration of each group, the animals were euthanized, the brains were dissected and cut using a vibratome. Following this, the Golgi technique was performed. For each animal, 10 pyramidal cells from the CA1 and CA3 region and 10 granule cells from the dentate gyrus (DG) were selected. Statistical analysis of the branching order of pyramidal neurons of CA1 and CA3 and granular cells of GD revealed a significant decrease in animals treated with CCl_4, but treatment with PBA prevented this loss of neuronal branches. The analysis of the LDT and the number of dendritic spines of CA1, CA3 and DG neurons showed a significant increase after

treatment with PBA compared to the group induced with CCl_4. Furthermore, a decrease in the number of dendritic spines in rats induced with CCl_4, but PBA attenuated the decline in the number of dendritic spines in the 3 analyzed regions of the hippocampus. Our results show that CCl_4 causes changes in neuronal morphology, but we suggest that PBA may play a fundamental role in the development of HE, which is why it should be considered as a therapeutic alternative for this population and thus allow them to improve their quality of life.

Disclosures: D. Juárez Serrano: None. **G. Flores:** None. **M. Munoz Arenas:** None. **D. Torres Cifuentes:** None. **I. Cesar Arteaga:** None. **J. Moran Perales:** None. **A. Diaz:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.02/C69

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: economic scholarship-PROCIENCIA

Title: Determination of the expression of pro- and anti-inflammatory cytokines by rt-qpcr, in primary astrocytic and mixed cultures, incubated with E/S antigens and total cysticercus stage of t.solium

Authors: *K. J. GONZALES MALPARTIDA, Jr;
Univ. Peruana Cayetano, lima, Peru

Abstract: Neurocysticercosis (NCC) is a disease caused by the larval stage (cyst or cysticercus) of Taenia solium, it is located at the level of the central nervous system (CNS). The cysticercus, when viable, usually activates a mild to moderate inflammatory response, which is exacerbated when the parasite degenerates or dies. Much of this exacerbated response depends on the excretory/secretory (E/S) and total (T) antigens of the parasite. This response in immune modulation remains conserved in most Helminths. Neuronal and glial cells play an important role in the regulation of inflammation. Studies have shown that there is an association between inflammation and the characteristic symptoms of NCC, which mainly include epilepsy. The high expression of pro- and anti-inflammatory cytokines (IL-1β, IL-10,TGFβ) produced mainly by astrocytes and microglia within the CNS has been linked to numerous pathologies and damage models. However, in NCC there is not enough information about the degree of expression of these cytokines in vitro. The present investigation will focus on determining the expression of pro- and anti-inflammatory cytokines in primary mixed and Astrocytic culture of rat brain. Both cultures incubated with E/S and T antigen of the cysticercus stage of the T.solium parasite. Achieving a better understanding of the mechanisms underlying NCC disease would allow us to find therapeutic targets that can reduce or inhibit the inflammation in the brain produced by the parasite and counteract the adverse effects of current drugs such as Albendazole - Praziquantel.

Disclosures: K.J. Gonzales Malpartida: None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.03/C70

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R03 AG070766
NIH Grant R01 EY027881
NIH Grant RO1 NS066019
NIH Grant P30 HD 018655

Title: Superoxide derived from mitochondrial metabolism and not NADPH oxidase underlies heightened vulnerability to excitotoxic injury in hippocampal slices from the neuronal GLT-1 knockout mouse

Authors: *P. A. ROSENBERG[1], J. WANG[1], J. V. ANDERSEN[2], B. I. ALDANA[2], B. ZHANG[1], E. V. PROCHOWNIK[3], S. LI[4];
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Abstract: We have previously reported a failure of functional recovery in the CA1 region of acute hippocampal slices from mice with a conditional neuronal knockout of GLT-1 driven by synapsin-Cre (synGLT-1 KO). The failure of recovery is due to excitotoxic injury. We hypothesized that changes in mitochondrial metabolism contribute to the heightened vulnerability in the synGLT-1 KO mice. Here we combined biochemical, molecular, metabolic, and metabolomic studies with electrophysiology in hippocampal slices to understand the underlying mechanisms. We found impaired flux of carbon from ^{13}C-glucose into the tricarboxylic acid (TCA) cycle in synGLT-1 KO slices, downregulation of the neuronal glucose transporter GLUT3, and compromised glycogen recovery during *ex vivo* incubation. Supplementing incubation media during recovery with 20 mM D-glucose normalized glycogen recovery, but had no effect on functional recovery. In contrast 20 mM non-metabolizable L-glucose substantially improved slice recovery, suggesting that D-glucose metabolism contributes to the injury in the synGLT-1 KO slices. L-lactate substitution for D-glucose did not promote recovery, implicating mitochondrial metabolism. Consistent with this hypothesis, phosphorylation of pyruvate dehydrogenase (PDH), which decreases enzyme activity, was increased in wild-type (WT) slices during the recovery period, but not in synGLT-1 KO slices. Since metabolism of glucose by the mitochondrial electron transport chain is associated with superoxide production, we tested the effect of drugs that scavenge and prevent superoxide production. The superoxide dismutase/catalase mimic EUK-134 conferred complete protection. A site-specific inhibitor of complex III superoxide production, S3QEL-2, was also protective, but inhibitors of NADPH oxidase were not. In summary, we have obtained evidence that metabolic glucose utilization is toxic to synGLT-1 KO slices and that this toxicity is mediated by

production of superoxide by mitochondrial metabolism. We hypothesize that reprogramming of glucose utilization contributes to the functional recovery routinely observed in slices from WT animals, and that maintenance of carbon flux derived from glucose through the TCA cycle, likely to be an adaptive response to metabolic abnormalities imposed by inactivation of neuronal GLT-1, mediates the increased sensitivity to excitotoxicity seen in slices from these mice.

Disclosures: P.A. Rosenberg: None. **J. Wang:** None. **J.V. Andersen:** None. **B.I. Aldana:** None. **B. Zhang:** None. **E.V. Prochownik:** None. **S. Li:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.04/C71

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Takeda Science Foundation
The Smoking Research Foundation

Title: The neuroprotective effects of activated fibroblast growth factor receptor against dipeptide repeat proteins mediated toxicity

Authors: *T. ITO, K. OHUCHI, H. KURITA, M. INDEN;
Gifu Pharmaceut. Univ., Gifu-shi / Gifu, Japan

Abstract: Amyotrophic lateral sclerosis (ALS) is an adult-onset neurological disorder that is characterized by muscle weakness and atrophy, paralysis, and eventual death by respiratory failure. Symptoms result from the selective degeneration of upper and lower motor neurons. Currently, there is no clearly effective treatment or cure for this disease. The most frequent genetic cause of ALS is a GGGGCC hexanucleotide repeat expansion in the first non-coding region of the chromosome 9 open reading frame 72 gene (C9orf72). This mutation results in repeat-associated non-AUG (RAN) translation of dipeptide repeat proteins (DPRs) and accumulate DPRs in cell. Among DPRs, poly-proline-arginine (PR) accumulates in the nucleus and causes higher cytotoxicity than other DPRs. Furthermore, the accumulation of p53 tumor suppressor (p53) and the resulting increased stress are known to be one of the toxic mechanisms of poly-PR. Fibroblast growth factor receptor (FGFR) is a receptor tyrosine kinase involved in cell proliferation, differentiation, and survival. Activation of FGFR shows effects such as neurogenesis and inhibition of apoptosis. Additionally, activation of FGFR is known to induce activation of Murine Double Minute-2 (MDM2), which is involved in p53 degradation, through PI3K-Akt pathway. However, there are no reports of FGFR-mediated neuroprotective effects against Poly-PR induced toxicity. Therefore, in this study, we investigated the neuroprotective effects of FGFR activation in neurons by using Poly-PR transfected cells. In the present study, we transfected NSC34, a mouse motor neuron-like cell, with GFP- fused Poly-PR and treated with FGF2, a ligand for FGFR1. In result, we found that FGFR activation by FGF2 treatment

exhibited significant neuroprotective effects against Poly-PR induced toxicity. The neuroprotective effect of FGF2 treatment was inhibited by pretreatment with LY294002, a PI3K inhibitor, and suggested the involvement of the PI3K-Akt pathway. In addition, FGF2 treatment caused an increase in MDM2 expression and suppressed p53 accumulation in Poly-PR-transfected cells. These results suggested that activation of FGFR suppresses p53 accumulation through MDM2 and exhibits neuroprotective effects.

Disclosures: T. Ito: None. **K. Ohuchi:** None. **H. Kurita:** None. **M. Inden:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.05/C72

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: The Smoking Research Foundation
Takeda Science Foundation

Title: Mitophagy disfunction and mitochondrial damage resulted in disruption of iron homeostasis in PARK9

Authors: *T. MURAKAMI, K. OHUCHI, H. KURITA, M. INDEN;
Gifu Pharmaceut. Univ., Gifu-shi / Gifu-ken, Japan

Abstract: Background and Purpose: Iron accumulation in the substantia nigra (SN) may be significant in Parkinson's disease (PD), but the underlying mechanism is unclear. Although iron is an essential element, excessive amounts produce toxicity. We focused on the role of iron and ATP13A2, the causative gene of PARK9 neurodegeneration with brain iron accumulation. ATP13A2 is an ATPase localized in the lysosome and is thought to maintain lysosome homeostasis by transporting cationic molecules such as polyamines, protons, and metal ions across the membrane. Additionally, we reported the disruption of intracellular iron homeostasis by suppressing ATP13A2 expression. In patients with PD, there is a high lysosomal pH caused by loss-of-function mutations of ATP13A2, leading to proteolytic failure. Therefore, considering that mitophagy is a lysosome-mediated mechanism, decreased ATP13A2 function can result in mitophagy failure. Mitochondria may be key in the pathogenesis of PARK9. In this study, we attempted to elucidate the relationship between mitochondria and the disruption of iron homeostasis. **Methods:** We generated PARK9 model cells by ATP13A2 knockdown in human neuroblastoma SH-SY5Y, and analyzed heme synthesis, IRP2 expression, mitochondrial morphology, and mitophagy. Mitochondrial morphology and mitophagy were analyzed by probes. mtDNA leak to cytosol was estimated for mitochondrial damage.**Results and Discussion:** Intracellular iron levels are maintained through an IRP2-based iron-responsive feedback system that regulates the expression of iron-related genes to prevent cytotoxicity. Therefore, we analyzed IRP2 expression with or without ferric ammonium citrate (FAC)

treatment. FAC treatment decreased IRP2 levels in control cells but not in PARK9 model cells, suggesting that intracellular iron levels increased by ATP13A2 knockdown, but IRP2 did not respond to the upregulation of labile iron. Next, we assessed the capacity of heme synthesis, as IRP2 degradation is induced by heme upregulation in mitochondria. The results showed that heme synthesis was decreased in PARK9 model cells. Additionally, we observed abnormal mitochondrial morphology and leakage of mtDNA into the cytosol. The leakage of mtDNA is associated with apoptosis. Furthermore, the capacity of mitophagy was decreased, indicating an accumulation of damaged mitochondria. Therefore, it is possible that mitochondrial dysfunction may contribute to the disruption of intracellular iron homeostasis in PARK9 model cells.

Disclosures: T. Murakami: None. **K. Ohuchi:** None. **H. Kurita:** None. **M. Inden:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.06/C73

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Takeda Science Foundation
The smoking Research Foundation

Title: Effects of activated α7 nicotinic acetylcholine receptor against α-synuclein-induced neurotoxicity.

Authors: *S. TAKIZAWA, K. OHUCHI, T. ITO, T. MURAKAMI, H. KURITA, M. INDEN; Gifu Pharmaceut. Univ., Gifu, Japan

Abstract: Increasing evidence indicates that certain neurodegenerative diseases, including Parkinson's disease (PD), involve the loss of neuronal nicotinic acetylcholine receptors (nAChRs). Among these receptors, α7 nAChR have emerged as crucial targets in the development of PD therapeutics. Previously, we demonstrated that α7 nAChR activation protects against nigrostriatal dopamine degeneration in acute and chronic PD animal models induced by 6-hydroxydopamine and rotenone, respectively. Additionally, we revealed that α7 nAChR activation exerts multiple neuroprotective effects, including autophagy activation in a cellular model of amyotrophic lateral sclerosis. However, the precise mechanisms underlying these neuroprotective effects remain to be elucidated. Although the exact mechanisms underlying PD remain unclear, α-synuclein (α-Syn, encoded by *SNCA*), a primary component of the cytoplasmic inclusions known as Lewy bodies, is a major contributor to PD pathophysiology. Additionally, *SNCA* gene mutations and multiplications can alter α-Syn aggregation potential. These mutations cause autosomal dominant PD in a dose-dependent manner. They include amino acid substitutions, such as A53T, A30P, and E46K, as well as gene duplication and triplication events. In previous research, we successfully established novel cell lines (α-SynWT-N2a, α-SynA30P-N2a, and α-SynE46K-N2a cells) that stably express α-Syn proteins. In these cells,

upregulation of wild-type α-Syn or mutant-type α-Syn occurs upon exposure to cumate, a chemical compound inducer. However, the effects of α7 nAChR activation on α-Syn-induced neurotoxicity have not been established. In the present study, we investigated whether PNU282987, a selective α7 nAChR agonist, exerts neuroprotective effects against α-Syn-induced neurotoxicity in α-Syn-N2a cells. We found that α7 nAChR activation by PNU282987 promotes neuroprotection against α-Syn neurotoxicity by stimulating autophagy through transcription factor EB. These results reveal a novel neuroprotective mechanism associated with α7 nAChR and offer valuable insights into the development PD therapeutic agents.

Disclosures: S. Takizawa: None. **K. Ohuchi:** None. **T. Ito:** None. **T. Murakami:** None. **H. Kurita:** None. **M. Inden:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.07/C74

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: the Smoking Research Foundation
Takeda Science Foundation

Title: Rotenone induces neuroinflammation via the cGAS/STING/type I IFN pathway

Authors: *A. FUJIMAKI, T. MURAKAMI, K. OHUCHI, H. KURITA, M. INDEN;
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Abstract: Cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS), a DNA sensor, detects foreign DNA, such as viruses, and activates stimulator of interferon genes (STING) to elicit a type I interferon (IFN) response and subsequent induction of inflammatory cytokine expression. However, the response of cGAS to mitochondrial DNA (mtDNA) leaking into the cytoplasm causes sustained activation of the cGAS/STING pathway. This activation contributes to age-related chronic inflammation and the inflammatory pathogenesis of multiple neurodegenerative diseases, including amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease (PD). PD is characterized by the loss of dopaminergic neurons in the substantia nigra, and mitochondrial dysfunction has been implicated in PD. In previous studies, increased type I IFN was observed in postmortem PD human samples and PD model mice. One study suggested that the loss of STING prevented inflammation and dopaminergic neuron degeneration in a mouse model of PD. Most studies on cGAS/STING in the brain have focused on microglia. However, the contribution of the cGAS/STING pathway via mitochondrial damage in neurons remains unclear. In the present study, we evaluated cGAS/STING activity in SH-SY5Y cells upon exposure to rotenone, an inhibitor of complex I of the mitochondrial electron transport chain used to generate PD models in experimental animals. Exposure to rotenone increased mtDNA in the cytoplasm, signaling through phosphorylation of the cGAS/STING

pathway was observed, and finally, type I interferon was elevated. These activations of cGAS/STING pathway by rotenone occurred at treatment concentrations of rotenone that did not cause cell death. cGAS/STING activation by rotenone occurred at rotenone concentrations that did not cause cell death. In addition, rotenone-induced elevation of type I IFN was inhibited by inhibitors of the cGAS/STING pathway. These findings indicate that mitochondrial damage in neurons causes inflammation via the cGAS/STING/type I IFN pathway. In addition, we found that certain natural compounds inhibit cGAS/STING pathway. These results suggest that inhibition of cGAS/STING/type I IFN pathway may have novel therapeutic potential for PD.

Disclosures: A. Fujimaki: None. **T. Murakami:** None. **K. Ohuchi:** None. **H. Kurita:** None. **M. Inden:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.08/C75

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Natural Science Foundation of China
National Key Research and Development Program of China

Title: Selective neurodegeneration and its mechanisms in HD knock-in pigs

Authors: *J. LI[1,2], Y. LIN[1,2], S.-H. LI[1,2], X. LI[1,2], S. YAN[1,2];
[1]Jinan Univ., Guang Zhou, China; [2]Guangdong Key Laboratory of Non-human Primate Research, GHM Institute of CNS Regeneration, School of Medicine, Guang Zhou, China

Abstract: Immune infiltration of T cells in the brain has been observed in various pathological conditions, including Alzheimer's disease (AD) and Parkinson's disease (PD), and infiltrating T cells are linked with neurodegeneration. However, whether immune infiltration of T cells occurs in Huntington's disease (HD) and the relationship between T cells and neurodegeneration in HD remain unclear. To address this question, we conducted an investigation using HD knock-in pigs, which exhibit selective neurodegeneration similar to HD patients. Initially, we established the first single-cell atlas of the HD knock-in pig striatum, thereby laying the foundation for investigating potential pathogenic mechanisms of HD at the single-cell level. Cross-species single-cell transcriptomic analysis revealed significant parallels in cellular composition and proportions between the pig and human striatum, underscoring the importance and necessity of using pigs as animal models for investigating HD. Single cell nuclear RNAseq analysis revealed that HD knock-in pigs recapitulate the loss of specific types of striatal neurons (mainly spiny projection neurons) observed in HD patients, a phenomenon not observed in HD knock-in mice. The increased IFITM3$^+$ interferon (IFN)-associated microglia subgroup in HD knock-in pigs was found to secrete CCL8 chemokines to recruit CD8$^+$ T cells. Infiltrating T cells release perforin and granzyme, leading to the degeneration of striatal neurons. Although HD knock-in mouse

striatum does not show elevated CCL8, administration of CCL8 resulted in an increase in $CD8^+$ T cells and more severe neurodegeneration similar to that observed in the HD knock-in pig brain. These findings suggest that the effects of mutant huntingtin on species-dependent disease-associated microglial subtypes contribute to microglia-driven immune infiltration of $CD8^+$ T cells, ultimately playing a critical role in the selective neurodegeneration in HD.

Disclosures: J. Li: None. **Y. Lin:** None. **S. Li:** None. **X. Li:** None. **S. Yan:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.09/C76

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NEI Core Grant P30 EY030413

Title: Preventing the Death of Injured CNS Neurons by Intervening Long Noncoding RNAs

Authors: *N. C. MATHEW[1], K. LEVAY[2], A. AYUPE[3], Y. HU[4], K. K. PARK[1];
[1]Ophthalmology, Dept. of Neuroscience, Peter O'Donnell Jr. Brain Inst., UT Southwestern Med. Ctr., Dallas, TX; [2]Neurolog. Surgery, The Miami Project to Cure Paralysis, [3]Sylvester Comprehensive Cancer Ctr., Univ. of Miami Miller Sch. of Med., Miami, FL; [4]Ophthalmology, Stanford Univ., Palo Alto, CA

Abstract: Preventing the Death of Injured CNS Neurons by Intervening Long Noncoding RNAs,,,,,.
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• Long noncoding RNAs (lncRNAs) are a new frontier in the realm of gene regulation. With the advancements in high-throughput RNA sequencing, lncRNAs are a target of interest in different disease and injury models. Injury to the optic nerve induces different transcriptomic profiles between the subsets of retinal ganglion cells (RGCs), including lncRNA expression. A long intergenic lncRNA which we call optic nerve induced lncRNA-1 (Onil1) is upregulated in certain RGCs post insult to the optic nerve both in optic nerve crush (ONC) and retinal ischemia models. Prevention of Onil1 expression provides neuroprotection of RGCs after ONC. Identifying expression and neuroprotective capabilities through silencing of Onil1 expression in other clinically relevant models would solidify Onil1 as a target of interest in RGC loss prevention. We seek to verify Onil1 expression in a closed angle glaucoma model and verify upregulation of Onil1 expression in specific subtypes of RGCs. We verify neuroprotection of RGCs in these models through silencing Onil1 expression through intravitreal injection of a small-hairpin RNA (shRNA) and quantify RGC survival through immuno-histochemistry analysis. We examined the DNA and protein binding partners of Onil1 through chromatin isolation through RNA purification. The binding partners of Onil1 may provide insight on the role Onil1 has on gene regulation. To help further identify which genes are affected by Onil1

expression, we perform bulk RNA sequencing of RGCs whose expression of Onil1 has been manipulated through shRNA treatment in the ONC model. By identifying which gene Onil1 regulates, a better understanding of the mechanism behind RGC loss due to optic nerve injury will be gained, and further methods of RGC loss prevention can be generated. The goal of this project is to verify Onil1 expression in multiple injury/disease models to show its prevalence in RGC loss, and to better understand the mechanisms by which Onil1contributes to neuronal loss after injury.

Disclosures: N.C. Mathew: None. **K. Levay:** None. **A. Ayupe:** None. **Y. Hu:** None. **K.K. Park:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.10/C77

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Rhode Island Medical Research Foundation
Roddy Foundation
Plastics Initiative, University of Rhode Island
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Rhode Island Institutional Development Award (IDeA) Network of Biomedical Research Excellence from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P20GM103430
George & Anne Ryan Institute for Neuroscience, University of Rhode Island

Title: Interplay Between Microplastic Exposure, Genetic Risk Factors, and Cognitive Decline

Authors: L. GASPAR, S. BARTMAN, H. TOBIAS-WALLINGFORD, G. COPPOTELLI, *J. M. ROSS;
George and Anne Ryan Inst. for Neurosci.; Col. of Pharm., Univ. of Rhode Island, Kingston, RI

Abstract: As the global population continues to rise, so too has the consumption of material goods. One of the most common commodities on the market in recent decades is plastics, with their global production reaching 460 million tons in 2019, and continuing to grow almost exponentially. Despite the societal advancements plastics have allowed, the mismanagement of plastic waste has become a pressing global issue, especially the leakage of microplastics (MPs). Microplastics (plastic particles <5mm in size) have been shown to induce negative health outcomes such as oxidative stress, inflammation, and decreased cell viability in marine organisms. Current research suggests that these MPs may be transported throughout the environment, however research into their overall health effects, especially in mammals, is still

limited. Moreover, minimal research has been done to study the effects of MPs in models of disease. This has led our group to explore the biological and cognitive consequences of 0.1 and 2 µm pristine polystyrene MPs (PS-MPs) exposure using a humanized knock-in APOE4 mouse model to assess the interaction between MPs exposure and genetic risk factors of neurological disease. Following a three-week exposure to water treated with the fluorescently-labeled PS-MPs, young (3-6 mos) female and male h-APOE3 and h-APOE4 mice were assessed using behavioral assays such as open-field, light/dark preference, EPM, Y-maze, and novel object recognition, followed by tissue analyses such as Western blot and immunohistochemistry. Data from these assays suggests that short-term exposure to microplastics induced behavioral changes predominantly in APOE4 mice in a sex-dependent manner and that the APOE4 allele may exacerbate other adverse outcomes following exposure. These findings suggest the need for further research to better understand the mechanisms by which MPs may interact with genetic risk factors to accelerate neurological disease progression.

Disclosures: L. Gaspar: None. **S. Bartman:** None. **H. Tobias-Wallingford:** None. **G. Coppotelli:** None. **J.M. Ross:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.11/C78

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Mary S. Kostalos and John Kostalos, Jr. Fund

Title: Cytotoxic and neuroprotective effects of stress hormones in SH-SY5Y neuroblastoma cells

Authors: *V. Y. RAMIREZ, J. A. SIERRA FONSECA;
Sci., Chatham Univ., Pittsburgh, PA

Abstract: Neurodegenerative disorders, such as Alzheimer’s disease (AD), are marked by an abnormal aggregation of proteins, notably hyperphosphorylated tau and amyloid beta (Aβ) peptides. While the exact cause of sporadic AD remains unknown, environmental factors, particularly chronic stress, have emerged as potential contributors to disease onset and progression. The hypothalamic-pituitary-adrenal (HPA) axis mediates the response to chronic stress through a cascade of signals. This involves the activation of neurons in the paraventricular nucleus of the hypothalamus, which releases corticotrophin-releasing factor (CRF). This hormone then stimulates the anterior pituitary to secrete adrenocorticotropic hormone, leading to glucocorticoid secretion (GC). Cortisol, the primary GC in humans, shows a seeming correlation with disease progression and dementia severity in AD. While prolonged exposure to stress hormones, particularly cortisol, is often associated with harmful effects, CRF is believed to have neuroprotective properties. Thus, we hypothesized that exposure to CRF would exert

neuroprotective effects against chronic cortisol exposure. This study aims to clarify the impact of cortisol and CRF, on AD pathogenesis using a widely validated in vitro neuronal cell model, SH-SY5Y neuroblastoma cells. We employed cytotoxicity assays to comprehensively assess the effects of increasing concentrations of cortisol (0.1-50 µM) and CRF (0.1-5 µM) on neuroblastoma cell viability. Cells were exposed to stress hormones (individually or concomitant exposure) for 24 hours, and cytotoxicity was measured using a resazurin-based reagent. One-way ANOVA revealed that two concentrations of cortisol (0.1 and 50 µM) exerted significant cytotoxicity ($p<0.05$). Conversely, exposure to CRF significantly ($p<0.05$) increased cell viability at 0.5 µM and 1 µM concentrations. Concomitant exposure to both cortisol and CRF did not yield any statistically significant differences at lower cortisol concentrations, suggesting a reversal of cortisol-induced cytotoxicity by CRF. However, concomitant exposure to 20 µM cortisol and 1 µM CRF for 24 hours did significantly decrease viability. Collectively, our findings reveal that CRF may have the ability to mitigate the cytotoxicity induced by cortisol, but concentration-specific effects may also be present. Ongoing investigations are focused on further studying these phenomena, as well as on unraveling the molecular mechanisms underlying the interplay between stress hormones and neuropathological markers of AD.

Disclosures: V.Y. Ramirez: None. **J.A. Sierra Fonseca:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.12/C79

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NINDS (3R15 NS095317-02A1S1)

Title: Evaluating the role of protein fragments in Neurodegeneration

Authors: *W. LOKUSO[1], G. M. RAMIREZ[1], E. NA[3], C. S. BROWER[2];
[2]Biol., [1]Texas Woman's Univ., Denton, TX; [3]Texas Woman's Univ., Denton, TX

Abstract: Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) are associated with protein misfolding and aggregation. Our research focuses on the human TAR DNA-binding protein 43 (TDP43), which is strongly linked with ALS, FTD, and other forms of dementia. TDP43 is vulnerable to proteolytic cleavage resulting in several aggregation-prone fragments. Although the loss of full-length TDP43 function has been shown to contribute to disease, we hypothesize that the proteolytic fragments of TDP43 also contribute to disease through a toxic gain-of-function mechanism. To directly test this, we expressed disease-associated TDP43 fragments in the upper motor cortex of mice that retain intact (non-cleaved) TDP43 and examined these mice for motor defects. Our results indicate that the expression of specific TDP43 fragments in the mouse motor cortex leads to defects in motor coordination and balance.

Disclosures: W. Lokuso: None. **G.M. Ramirez:** None. **E. Na:** None. **C.S. Brower:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant P30GM100329
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Title: Endolysosome iron chelation and acidification block nicotine- and ethyl alcohol-induced cytotoxicity

Authors: *P. HALCROW, **J. D. GEIGER**;
Biomed. Sci., Univ. of North Dakota Sch. of Med. and Hlth. Sci., Grand Forks, ND

Abstract: Nicotine and ethyl alcohol (EtOH) are commonly consumed psychoactive drugs. As legal but regulated drugs, nicotine and EtOH adversely affect the health of people consuming them. Nicotine and EtOH increase levels of reactive oxygen species (ROS) and cause neurotoxicity but by unknown mechanisms. Ferrous iron (Fe^{2+}) is well known to increase levels of ROS via Fenton-like chemistry, and endosomes and lysosomes (endolysosomes) contain high levels of readily releasable [Fe^{2+}] that, when released, are sufficient to affect cytosolic and mitochondrial Fe^{2+} and ROS levels. Endolysosome acidity maintains iron homeostasis, and endolysosome de-acidification triggers Fe^{2+} release from endolysosomes and Fe^{2+} accumulation in the cytosol and mitochondria; nicotine and EtOH de-acidify endolysosomes. Although well-known as an antioxidant, deferoxamine (DFO) is an endolysosome-specific iron chelator that binds ferric iron (Fe^{3+}), induces Fe^{2+} to Fe^{3+} oxidation, and increases [H^{+}]. In addition, endolysosome acidification via mucolipin synthetic agonist 1 (ML-SA1) inhibits endolysosome de-acidification-induced neurotoxicity. Thus, it was important to determine how DFO and ML-SA1 affect the intraluminal chemistry of endolysosome iron and, accordingly, identify mechanisms by which nicotine and EtOH induce neurotoxicity. Using SH-SY5Y neuroblastoma cells and U87MG astrocytoma cells we showed that nicotine and EtOH (1) de-acidified endolysosomes, (2) decreased endolysosome Fe^{2+} levels, (3) increased cytosolic and mitochondrial Fe^{2+} and ROS levels, (4) depolarized mitochondrial potentials, and (5) induced cell death; effects all blocked by DFO and ML-SA1. Understanding the role of endolysosome iron in nicotine- and EtOH-induced neurotoxicity may provide new insight into the pathological implications of these commonly used psychoactive drugs.

Disclosures: P. Halcrow: None. **J.D. Geiger:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

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Program #/Poster #: PSTR333.14/C81

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 1R44MH135526-01

Title: Multiplexed ipsc-derived neuron, astrocyte, and microglia tri-culture model for neurotoxicity screening: neuron excitability, mitochondrial membrane potential, and synapses.

Authors: *K. L. GORDON[1], C. G. RINES[2], N. A. SUAREZ[3], A. S. SMITH[4], P. MCDONOUGH[5], J. PRICE[6];
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Abstract: Current CNS preclinical models lack the predictivity, throughput, and cost-effectiveness required to accurately identify neuro-effective and neuro-safe drug candidates. Human induced pluripotent stem cell models (hiPSC) are a promising *in vitro* system for predictive assay development. Here, we show the development of an hiPSC-derived CNS tri-culture model containing neurons, astrocytes, and microglia for neurotoxicity testing. This multiplexed assay system will identify mechanisms of compound toxicity by assessing changes to neuron excitability and network connectivity (action potential-induced calcium activity), mitochondrial membrane potential (TMRM), and synapse density (synapsin1, PSD95, and β-III-tubulin staining). We have identified a set of compounds with known neurotoxic mechanisms to validate our assay system. Our compounds include the sodium channel agonist veratridine and the sodium channel antagonist tetrodotoxin (TTX). We have also included cancer drugs like vincristine and HIV anti-retroviral drugs like elvitegravir, which have links to cognitive impairment. For this study, we prepared tri-cultures of neurons, astrocytes, and microglia, all derived from the same donor iPSC line (BrainXell). After three weeks of culture in imaging-quality 384-well plates, we treated the cells with 7-point compound dose responses for 30 minutes (acute exposure) or 48 hours (chronic exposure), We then loaded the cells with nuclear dye (Hoechst), mitochondrial dye (TMRM), and calcium dye (Cal520). After compound treatment, we used the IC200 Kinetic Image Cytometer, Vala's high-throughput digital movie imaging and analysis platform, to perform single cell calcium and mitochondrial membrane potential analysis. Our inert negative control compound, acetaminophen, did not affect neuron calcium activity or mitochondrial membrane potential. By contrast, veratridine and elvitegravir decreased mitochondrial membrane potential, indicating neurotoxic effects. Veratridine, elvitegravir, TTX, and vincristine all altered neuronal excitability, reducing the number of active cells and the event frequency and altering the amplitude and duration of the neuronal calcium

transients. Our work demonstrates that our cell analysis system is a powerful tool to test compounds for neurotoxic effects on tri-cultures featuring neurons and glia cells from complex 2-D culture systems.

Disclosures: K.L. Gordon: None. **C.G. Rines:** None. **N.A. Suarez:** None. **A.S. Smith:** None. **P. McDonough:** None. **J. Price:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.15/C82

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: JSPS 23K24436
JSPS 23K21462
JSPS 22K19737
JSPS 22K16646
JSPS 23K21623

Title: Induction of Purkinje cell degeneration in mice after heat exposure

Authors: *H. OHTAKI[1], K. MIYAMOTO[2], K. SUZUKI[2], A. YOSHIKAWA[3], K. DOHI[2]; [1]Tokyo Univ. of Pharm. and Life Sci., Hachioji, Japan; [2]Emergency and Disaster Med., Showa Univ. Sch. of Med., Tokyo, Japan; [3]Div. of Hlth. Sci. Educ., Showa Univ., Yokohama/Kanagawa, Japan

Abstract: Global warming is a huge concern and induces to climate change in the earth. Due to the influence, the ambient temperature (AT) of summer has been considering to be increased. Especially, summertime in Japan is high in the relative humidity (RH) as well as AT and the risk of heatstroke indicating by Wet-Bulb Globe Temperature (WBGT) is extremely higher in Japan. Actually, the number of heatstroke patients yearly has been increasing. We recently developed a heatstroke model which exposed to high AT and RH, mimicking the environment of Japanese summer in mice. The animals were exhibited dehydration and electrolyte abnormality. Moreover, they exposed multiple organ failure in the livers, kidneys and intestines. However, the abnormality of the central nervous system (CNS) has not well-known despite to a number of patients showed CNS disorders. In present study, we examined to evaluate the effect of heat exposure on the CNS, especially cerebellum.The C57/BL6 strained mice which were dehydrated for 3 hours were exposed to AT (41℃) and RH (>99%) for 60 min with custom made heat stroke chamber (200 × 340 × 300 mm). after the heat exposure, the mice were kept for 1 week and access freely food and water. Some mice were collected blood for confirm serum biochemical parameters to confirm heat stroke. The mice were transcardially perfused with 10% neutralized formalin and the sagittal brains were sectioned as the paraffin sections. The brain was removed and divided into two parts along the longitudinal cerebral fissure. perfused cardinally with 10%

on time dependent fashion. The Purkinje cells which detected with Calbindin immunostaining were exhibited a round, plump and smooth surface before heat exposure. Immediately after the heat exposure, no obvious changes in the number and morphology of Purkinje cells in cerebellum. Also, no morphological changes in cerebral cortex and hippocampus as well. However, they were changed an irregular polygonal form and significantly decreased 96 hours after heat exposure. Confirming with HE staining, the degenerative neurons finally seemed to burst like morphology, and were negative for Fluoro Jede B and TUNEL, suggesting necrosis. During the experimental periods, no obvious changes were observed in the cerebral cortex and hippocampus. These results suggested the heat stress induced specifically necrotic neuronal cell death in the Purkinje cells of the cerebellum.

Disclosures: H. Ohtaki: None. **K. Miyamoto:** None. **K. Suzuki:** None. **A. Yoshikawa:** None. **K. Dohi:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

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Program #/Poster #: PSTR333.16/C83

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DA042156 from NIH (NIDA)

Title: Amphetamine Exposure during Embryogenesis increases reactive oxidative species in Adult C. elegans Animals.

Authors: *A. RAJOO[1,2], L. CARVELLI[1];
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Abstract: Amphetamine Exposure during Embryogenesis increases reactive oxidative species in Adult *C. elegans* Animals.
Andre Rajoo and Lucia Carvelli
Stiles-Nicholson Brain Institute and Harriet L. Wilkes Honors College, Florida Atlantic University, Jupiter FL 33458 USA
Amphetamine (Amph) is a psychostimulant used to treat a variety of diseases, including Attention Deficit Hyperactive Disorder (ADHD) and narcolepsy. However, due to the complexity of the mammalian brain, the mechanism of action underlying the addictive properties of Amph is still unknown. To overcome this problem, many labs use simpler organisms. In our lab we use *C. elegans* to study the effects of Amph at the dopaminergic synapses because the major key players of the dopaminergic system are highly conserved between *C. elegans* and humans. Recently, our lab showed that chronic exposure during embryogenesis with Amph generates adult animals that are hypersensitive to Amph. Here, we investigated whether AMPH given during embryogenesis causes oxidative stress in adult *C. elegans*. Using confocal microscopy, we collected immunofluorescent images from immobilized, but living, wild-type

animals previously treated with CellROX Orange, a cell permeable dye that marks reactive oxidative species (ROS). We also collected images from mutants, we created, expressing both mCherry labelled dopaminergic neurons and GFP-tagged SOD-3. Imaging data from animals labelled with the CellROX Orange dye or mCherry-GFP expressing animals show that embryos exposed to AMPH develop in adults with higher levels of ROS in the whole animal's body and in the dopaminergic neurons. However, when AMPH was combined with the ROS scavenging polyphenol Ellagic acid (EA), the AMPH-induced increase in ROS was significantly reduced both in the dopaminergic neurons and the whole animal's body. Finally, our behavioral studies show that EA also attenuated the AMPH-induced behavioral changes seen in adult animals exposed to AMPH during embryogenesis.

Disclosures: A. Rajoo: None. **L. Carvelli:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.17/C84

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Characterisation of in vitro neuronal and microglial disease models to support drug discovery efforts for neurodegenerative diseases

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Abstract: Neurodegenerative diseases are characterised by a progressive neuronal loss leading to a functional decline. Most frequent, age-related neurodegenerative disorders, Alzheimer's disease (AD) and Parkinson's disease (PD) affect millions of people worldwide, representing major unmet global health need. However, AD and PD drug development is held back due to the lack of reproducible in vitro models that can be used to screen and select disease-modifying therapeutics in a relatively inexpensive, efficient and fast fashion. The aim of the present study was to validate in vitro neuronal and microglial neurodegenerative disease models to enable screening of disease-modifying compounds for AD and PD. The pathophysiology of AD and PD was modelled in vitro by treating microglial (HMC3) and differentiated neuronal-like cells (SH-SY5Y) with pre-formed amyloid beta (Aβ) or alpha synuclein (αSyn) fibrils. The most common hallmarks of neurodegeneration were evaluated by performing aggregation, neurotoxicity, ROS production and phagocytosis assays. Incubation (24 hour) of Aβ-fibrils with the reporter Thioflavin-T (20 μM) lead to significant increases in fibril aggregation, confirming the fibrils suitability in subsequent assays. The HMC3 cells' phagocytic capacity was investigated by treatment with pHrodo labelled pre-formed fibrils and detected by an IncuCyte S3 Live-Cell Analysis System, while HMC3 and SH-SY5Y cell's viability was assessed using the MTT assay. Following Aβ or αSyn fibril treatment, the phagocytic capacity of HMC3 cells was significantly increased indicating the internalization of the fibrils. Simultaneous treatment with Aβ and

Aducanumab significantly increased the phagocytic capacity of the HMC3 cells compared to fibril treatment alone. 24-hour treatment with Aβ-42 and α-synuclein fibrils induced neurotoxicity in SH-SY5Y and HMC3 cells compared to the control condition. Similarly, Aβ fibrils induced significant increase ROS production in SH-SY5Y, which was rescued by co-treatment with the ROS scavenger Edaravone. To conclude, we show that our cellular neurodegenerative disease models focusing on fibril-induced cell toxicity, ROS production and phagocytosis can serve as a highly efficient tool to screen neurodegenerative disease-modifying drugs before screening in vivo.

Disclosures: M. Loos: A. Employment/Salary (full or part-time):; InnoSer.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.18/Web Only

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONACYT grant A1-S-21433 to PDM

Title: Effect of quinolinic acid administration on autophagy, apoptosis and necroptosis pathways.

Authors: *A. D. ENCISO OCEGUERA[1], P. MALDONADO[2], J. PEDRAZA CHAVERRI[3], C. A. SILVA-ISLAS[4];
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Abstract: Neurodegenerative diseases are characterized by the progressive loss of the neuronal population in specific regions of the brain due to different factors such as toxic metabolic disorders. In these diseases there are different biochemical mechanisms that play an important role in cellular and tissue damage, among which excitotoxicity is an important event in cell damage. Excitotoxicity is a mechanism of neuronal death caused by the overactivation of glutamate amino acid receptors, particularly those of the N-methyl-D-Aspartate (NMDA) subtype, causing the massive entry of Ca2+ through the plasma membrane, generating the deregulation of important pathways in the maintenance of cellular homeostasis such as autophagy.Autophagy is a degradative pathway that maintains cellular homeostasis through the degradation and recycling of cellular components. It has been observed that the administration of quinolinic acid (QUIN), an excitotoxic molecule, increases activation of autophagy and at the same time blocks the flow of autophagy (last stage of this pathway), in addition to the activation of different types of regulated cell death mechanisms such as apoptosis and necroptosis. In the

present work we evaluated, under an excitotoxic model of quinolinic acid, the different cell death pathways: autophagy, apoptosis and necroptosis. Male Wistar rats (260-300 g) were administered 1 μL of isotonic saline solution or 1 μL of QUIN equivalent to 120 and 240 nmol in the right striatum, then the cortex tissue was extracted 48 hours after QUIN administration. Finally, the proteins of apoptosis caspase-3 and Bax; autophagy p62 and cathepsin D; and necroptosis MLKL and RIP1 were quantified by Western Blot. The results show that after 48 hours of QUIN administration, the levels of caspase-3 and Bax in cortex tend to increase with 240 nmol, however this increase is not statistically significant. On the other hand, Cathepsin D and p62 show a decrease in its levels following both doses of QUIN administration. Additionally, in the necroptosis pathway, we only observed an increase in RIP1 with 120 nmol of QUIN. In conclusion these results suggest that striatal QUIN administration promotes alteration in autophagy pathway in the cortex at 48 h.

Disclosures: A.D. Enciso Oceguera: None. **P. Maldonado:** None. **J. Pedraza Chaverri:** None. **C.A. Silva-Islas:** None.

Poster

PSTR333: Cellular Stress and Degeneration

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Program #/Poster #: PSTR333.19/C85

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONACYT Grant A1-S-21433 to PDM

Title: The excitotoxic effect of quinolinc acid on the authophagy pathway in rat striatum

Authors: *M. MALDONADO GARCIA[1], M. BALAM LANDEROS[2], P. D. MALDONADO[3], J. PEDRAZA CHAVERRI[4], C. A. SILVA-ISLAS[5];
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Abstract: Excitotoxicity is a common mechanism of damage in neurodegenerative diseases. Is characterized by the overactivation of glutamate receptors, principally the N-methyl-D-aspartate (NMDA) subtype, resulting in the increase in the cytosol Ca^{2+} levels and the activation of different intracellular mechanisms associated with Ca^{2+} homeostasis disruption, that results in cell death. In particular, it has been observed that excitotoxicity promotes an imbalance in the autophagy pathway. Autophagy is a degradative pathway that removes misfolded proteins, damaged organelles, and long-lived proteins, and it is important for cell homeostasis. There are evidence suggesting that excitotoxicity is able to disrupt autophagy. Most works study this

pathway in the first 24 hours post excitotoxic event, however, the impact of excitotoxicity in autophagy at prolonged time intervals is poorly studied. On the other hand, striatal administration of quinolinic acid (QUIN) has been used as a model of excitotoxicity for the study of biochemical mechanisms involved in neurodegenerative diseases. We previously observed that QUIN induced a blockage in autophagy flux at 7 days, however at early times evidence of the effect of QUIN on autophagy flux is scarce. In this work, we evaluated the effect of striatal QUIN administration on the levels of protein on the autophagy pathway. We administered 1 µL of isotonic saline solution (ISS), 120 or 240 nmol of quinolinic acid (QUIN) in the right striatum of male wistar rats (280g to 320 g) and the striatum were collected at 4, 8, 24, 72 and 120 h. The levels of p62, preprocathepsin D and Cathepsin D were evaluated by western blot. We observed only an increase of p62 at 24 h after 120 nmol of QUIN administration, whereas the other proteins did not change at any evaluated time. These results suggest that autophagy can be disrupted only at 24 h after QUIN administration.

Disclosures: M. Maldonado Garcia: None. **M. Balam Landeros:** None. **P.D. Maldonado:** None. **J. Pedraza Chaverri:** None. **C.A. Silva-Islas:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.20/C86

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Methionine oxidation of clusterin in Alzheimer's disease and its effect on clusterin's binding to beta-amyloid

Authors: J. DODERER[1], *A. SMITH[2,3], J. SUBRAMANIAN[1], J. MOSKOVITZ[1]; [1]Dept. of Pharmacol. & Toxicology, Univ. of Kansas, Lawrence, KS; [2]Univ. of Kansas, Lawrence, KS; [3]Department of Pharmacology & Toxicology, University of Kansas, Lawrence, KS

Abstract: Clusterin is a secreted glycoprotein that participates in multiple physiological processes through its chaperon function. In Alzheimer's disease, the brain functions under an increased oxidative stress condition that causes an elevation of protein oxidation, resulting in enhanced pathology. Accordingly, it is important to determine the type of human brain cells that are mostly prone to methionine oxidation in Alzheimer's disease and specifically monitoring the methionine-oxidation levels of clusterin in human and mice brains and its effect on clusterin's function. We analyzed the level of methionine sulfoxide (MetO)-clusterin in these brains, using a combination of immunoprecipitation and Western-blot analyses. Also, we determine the effect of methionine oxidation on clusterin ability to bind beta-amyloid, *in vitro*, using calorimetric assay. Our results show that human neurons and astrocytes of Alzheimer's disease brains are mostly affected by methionine oxidation. Moreover, MetO-clusterin levels are elevated in postmortem Alzheimer's disease human and mouse brains in comparison to controls. Finally, oxidation of

methionine residues of purified clusterin reduced its binding efficiency to beta-amyloid. In conclusion, we suggest that methionine oxidation of brain-clusterin is enhanced in Alzheimer's disease and that this oxidation compromises its chaperon function, leading to exacerbation of beta-amyloid's toxicity in Alzheimer's disease.

Disclosures: J. Doderer: None. **A. Smith:** None. **J. Subramanian:** None. **J. Moskovitz:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.21/C87

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant DA051450

Title: Chronic methamphetamine increased mitochondrial density in substantia nigra pars compacta and locus coeruleus neurons in male but not female mice

Authors: *A. BHOWMIK[1], S. M. GRAVES[2];
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Abstract: Methamphetamine (meth) is an addictive and neurotoxic psychostimulant that increases monoamine oxidase (MAO)-dependent mitochondrial oxidative stress in substantia nigra pars compacta (SNc) dopamine and locus coeruleus (LC) norepinephrine neurons (Du et al., *Neuropharmacol* p.108817, 2021; Du et al., *Front Cell Neurosci* p.949923, 2022). Chronic administration results in SNc and LC degeneration in male mice, which is prevented by MAO inhibition (Du et al., *Neuropharmacol* p.108817, 2021; Du et al., *Front Cell Neurosci* p.949923, 2022) suggesting that meth-induced MAO-dependent mitochondrial stress drives degeneration. However, the impact of chronic meth on SNc and LC mitochondria is unclear. Acute binge (i.e. multiple moderate-to-high doses in one day) and *in vitro* studies provide evidence that meth impairs mitophagy (Moszczynska et al., *J Neurochem* p.1005, 2011; Lenzi et al., *Int J Mol Sci* p.8926, 2022). To determine the consequence of chronic meth on mitochondria in SNc and LC neurons, C57BL/6J mice were administered saline or meth (5 mg/kg; i.p.; n=4) for 14, 21 or 28 days. Sections entailing the entirety of SNc and LC were collected, and every sixth section stained for tyrosine hydroxylase (TH) to label SNc and LC neurons. Slices were counterstained for the voltage-dependent anion-selective channel protein 1 (VDAC1) to label mitochondria. *Z*-stacks (0.101 µm x 0.101 µm; 0.3 µm steps) of the soma of SNc and LC neurons were acquired and 3D reconstructions generated; mitochondrial density was calculated as the volume occupied by mitochondria (VDAC1 staining) divided by the total volume (TH staining); 12-20 SNc and 8-12 LC neurons were collected per mouse per group and data analyzed by nested *t*-tests or nested one-way ANOVA with Tukey's *post-hoc*. Mitochondrial density was increased in SNc and LC neurons of male mice after 21 (SNc: $p<0.0001$, LC: $p=0.0075$) and 28 days (SNc: $p<0.0001$, LC:

p=0.0044) of meth; MAO inhibition using rasagiline (1 mg/kg; i.p) prevents meth-induced SNc and LC degeneration (Du et al., *Neuropharmacol* p.108817, 2021; Du et al., *Front Cell Neurosci* p.949923, 2022) and prevented meth-induced changes in mitochondrial density. In contrast to male mice, female mice are resistant to meth-induced SNc and LC degeneration (Pilski & Graves, *Int J Mol Sci* p.13039, 2023). Similarly, we found that 28-day meth had no effect on SNc or LC mitochondrial density in female mice. These findings show that chronic meth causes an accumulation of mitochondria in neuronal populations vulnerable to degeneration; we hypothesize that this is an accumulation of dysfunctional mitochondria potentially resulting in a bioenergetic deficit.

Disclosures: A. Bhowmik: None. **S.M. Graves:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.22/C88

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NINDS R01 NS107398 (8/1/2019-7/31/2024), Supplement (1/1/2020-7/31/2021)
NIA/NINDS NRSA F30 NS124237

Title: Endoplasmic reticulum stress induces axon initial segment shortening via activation of the PERK pathway

Authors: *J. N. SHELBY[1], A. CHISHOLM[2], I. AKHMEDOV[2], K. SUSUKI[2];
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Abstract: Type 2 diabetes mellitus (T2DM) is an increasingly prevalent metabolic disorder highly associated with mild cognitive impairment and increased risk of dementia even with strict glucose control. We recently demonstrated the development of T2DM and impaired cognitive flexibility is associated with shortening of a specialized neuronal domain in the prefrontal cortex, the axon initial segment (AIS). The AIS regulates initiation of action potentials, and even subtle decrease in AIS length has been shown to decrease neuronal excitability. Understanding the mechanisms of AIS shortening and cognitive impairment in T2DM is required to develop treatments. Our research focuses on the role of endoplasmic reticulum (ER) stress, a cellular process implicated in the pathophysiology of diabetic brain complications, and subsequent activation of the unfolded protein response (UPR) PERK pathway. Previous studies indicate a key role of PERK activation in many neurodegenerative conditions. In this study, we hypothesized that ER stress mediates AIS shortening in diabetic conditions via the PERK pathway. Utilizing primary mouse cortical cultures after 10 days *in vitro*, immunofluorescence was used to visualize the AIS and length was quantified under blinded conditions. We show that sodium 4-phenylbutyrate (100 μM), a well-documented ER stress inhibitor, prevents the

14.9±3.4% AIS shortening induced by the T2DM factor methylglyoxal (100 μM, 24 hours). Exposure of cortical cultures to established ER stress inducer tunicamycin (TM; 0-1.0 μg/mL, 24 hours) induced dose-dependent reduction of AIS length without affecting neuronal viability. Because the 15.9±3.2% decrease in AIS length after 0.25 μg/mL TM exposure is similar to the AIS shortening previously demonstrated in mice with T2DM, we selected this dose to evaluate the role of the PERK pathway in ER stress-induced AIS shortening. Co-exposure to a PERK-specific inhibitor GSK2606414 (0.06 μM) prevented AIS shortening induced by TM. These results demonstrate ER stress is sufficient and necessary for AIS shortening *in vitro*. The PERK dependent nature of this AIS shortening supports the PERK pathway as a therapeutic target in T2DM related cognitive impairment.

Disclosures: J.N. Shelby: None. **A. Chisholm:** None. **I. Akhmedov:** None. **K. Susuki:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.23/C89

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/Arkansas INBRE Grant NIGMS P20 GM103429

Title: The presence of neurodegeneration-associated mutations increase sensitivity to reactive oxygen species in C. elegans

Authors: *R. D. FOSTER[1], D. DONLEY[2];
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Abstract: Oxidative stress is the broad term referring to the dysregulation of reactive oxygen species (ROS) leading to cell stress and eventual tissue damage. The buildup of ROS has been implicated in several neurodegenerative diseases, including Alzheimer's Disease (AD) and Amyotrophic Lateral Sclerosis (ALS). Both of these diseases have familial and genetic components but the impact of the relevant genetic mutations on oxidative stress is not well understood. Herein we characterize the response of *C. elegans* mutants in response to redox-active stressors, primarily metals. We previously found that a *C. elegans* model of AD was hyper-responsive to hydrogen peroxide stress compared to wild-type animals, which indicates that mutations associated with neurodegeneration alter the redox homeostasis. The present study reports the impact of amyloid beta overexpression in *C. elegans* on the development of oxidative stress as a way to explore the link between the deposition of amyloid species and the development of oxidative stress in AD. The increased oxidative stress that we observed in AD has also been implicated in ALS. One of the primary genes associated with familial ALS is the *C9orf72* gene which contains a GGGGCC hexanucleotide repeat expansion that results in pathology. We employ a *C. elegans* ALFA-1 mutant, which is a *C9orf72* ortholog and contains the repeat expansion found in human familial ALS. While the expansion is not naturally

occurring in the ALFA-1 gene, we utilize a transgenic mutant containing the pathological expansion. By comparing this mutant to wild-type and transgene control groups, we can elucidate the effect of the mutation on the ability of the organism to regulate ROS and respond to redox-active metals, such as iron and copper, which are commonly dysregulated in neurodegenerative disease. Determining the interaction between oxidative stress and neurodegenerative disease will help clarify how the role and regulation of ROS contribute to disease pathology. Further, these data strengthen our emerging understanding of mechanisms by which oxidative stress promotes neurodegenerative disease.

Disclosures: R.D. Foster: None. **D. Donley:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.24/C90

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: (NIH) grant R01EY005121 (NGB).

Title: Elovanoids attenuate lipid peroxidation in retinal cells confronted with oxidative stress

Authors: *R. M. PERERA[1], C. VAN LEEUWEN[2], J. M. CALANDRIA[3], N. G. BAZAN[4]; [1]Neurosciences Ctr. of Excellence, LSU Hlth. Sci. Ctr., New Orleans, LA; [2]Neurosci. Ctr. of Excellence, LSU Hlth. Sci. Ctr. New Orleans, New Orleans, LA; [3]LSUHSC, New Orleans, LA; [4]Neurosci. Ctr., Louisiana State Univ. Hlth. Scienc Interdisciplinary Neurosci. Training Program, New Orleans, LA

Abstract: Amyloid-beta peptide gathers in senile plaques within the brain affected by Alzheimer's disease. Similar conditions are evident in individuals with age-related macular degeneration (AMD). Moreover, elevated lipid peroxidation and inadequate antioxidant levels will result in an uncompensated oxidative stress (UOS) environment in both scenarios. Oxidized phospholipids (OxPLs) can induce harmful disturbances to the membranes of photoreceptor cells (PRC) and the retinal pigment epithelial cell (RPEC), thereby altering their structure and function. Due to high metabolic demands, RPE cells are under constant oxidative stress. Elovanoids (ELVs) represent a unique group of lipid mediators crucial for preserving the integrity of photoreceptor cells. They are di hydroxilated derivatives of very long-chain polyunsaturated fatty acids (VLC-PUFAs) C32:6 n3 and C34:6 n3. Here, we present a study on ELV biosynthesis and the enhanced cell survival under uncompensated oxidative stress conditions in RPEC. We have identified OxPL species in RPEC under UOS conditions via comprehensive untargeted lipidomic approach using liquid chromatography-tandem mass spectrometry (LC-MS/MS). RPEC were exposed to UOS, +/- ELV-N34 precursor (FA 34:6 n3). Extracted lipids were analyzed by LC-MS/MS for oxidized phospholipid species using untargeted lipidomics. Automatic data-processing, including peak assignments and

deconvolution of MS/MS data were carried out using MS-DIAL software. The resulting data were then compared with a reference library containing known oxidized lipid compounds. Cell viability was assessed using a Incucyte Live-Cell Analysis system. Western blot analysis was performed to follow Iduna protein abundance. Under UOS conditions, high levels of OxPLs, were observed, with the majority being oxidized phosphatidylethanolamine followed by oxidized phosphatidylcholine. Oxidized lipid profiles of RPEC treated with ELV-N34 precursor showed decreased levels compared to UOS samples. Also, Both ELV - N34 and mono hydroxylated intermediates were upregulated with FA supplementation under oxidative stress conditions. Our data demonstrate the active biosynthesis of ELV - N34 under oxidative stress conditions and protective role of this lipid mediator in preventing oxidation of phospholipid species. Therefore, ELV would likely to involve in regulatory functions of lipid peroxidation that may include targeting ferroptosis. Research support from the National Eye Institute (NIH) grant R01EY005121 (NGB).

Disclosures: R.M. Perera: None. **C. Van Leeuwen:** None. **J.M. Calandria:** None. **N.G. Bazan:** None.

Poster

PSTR333: Cellular Stress and Degeneration

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Program #/Poster #: PSTR333.25/C91

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01MH109382

Title: A commonly occurring PERK haplotype with modest but increased kinase activity results in elevated endoplasmic reticulum stress response and reduced stress tolerance in neuroglia

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Abstract: PERK is a pivotal regulator of the endoplasmic reticulum (ER) stress response and crucial in managing unfolded/misfolded proteins and excessive Ca2+ efflux from ER, playing a central role in the unfolded protein response (UPR) and integrated stress response. Dysregulation of PERK and UPR signaling is implicated in various neurodegenerative disorders. EIF2AK3, encoding PERK, harbors three common exonic single nucleotide variants (SNVs), forming the PERK-B haplotype that is prevalent in 28% of the global population, compared to PERK-A, present in 62% of the global population. UPR regulates stress response and preconditions cells to physiological stressors, including additional ER stress. Studies have shown that low/mild ER stress can trigger an adaptive response and is beneficial in the survival of cells challenged with a

subsequent stressor, in a phenomenon termed hormesis or stress tolerance. In this study, we utilized triple knock-in mice expressing the three exonic SNVs forming the PERK-B haplotype (PERK-B/B) and wild-type mice (PERK-A/A) to investigate the specific effects of the PERK-B haplotype on stress response and stress tolerance in neurons, neuroglia, and astrocytes. We hypothesized that the PERK-B would lead to augmented stress response but diminished stress tolerance. We aimed to reveal insights into PERK-mediated stress pathways and potential therapeutic strategies targeting PERK and UPR signaling in neurodegenerative diseases. Using thapsigargin as an ER stress inducer, we observed differences between PERK-B/B and PERK-A/A mice in vivo, suggesting compensatory mechanisms. In vitro, PERK-B/B neuroglia showed altered activation kinetics and transient CHOP elevation, indicating shifts towards maladaptive outcomes. PERK-B/B astrocytes exhibited enhanced activity and increased interleukin-6 secretion, hinting at altered stress response pathways. While neurotoxicity remained comparable, PERK-B/B neuroglia displayed reduced stress tolerance influenced by astrocytes, underlining cell-type-specific interactions and neuronal outcomes. Our findings contribute to understanding susceptibility to neurodegenerative diseases and highlight targeting PERK signaling for therapeutic interventions aimed at enhancing stress resilience in the CNS. This study emphasizes genetic influences on stress response pathways for developing targeted therapies, informing potential strategies targeting PERK and UPR signaling in chronic diseases, and understanding the role of PERK haplotype variations in cellular stress responses and stress tolerance.

Disclosures: S. Ghura: None. **J.K. Arya:** None. **E. Alvarez Periel:** None. **S.B. Newton:** None. **C. Akay-Espinoza:** None. **K.L. Jordan-Sciutto:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.26/C92

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: GRANT TO LARC – CONAHCYT FELLOWSHIP:1319432

Title: Effect of exogenous serotonin and dopamine on ovoposition in adult C. elgans subjected to oxidative stress by H_2O_2

Authors: *L. RAMIREZ CONTRERAS[1], D. AGUILAR OCAMPO[2], M. REVELES GONZÁLEZ[1], M. MACÍAS-CARBALLO[3], S. SANCHEZ[1], S. HERNÁNDEZ ESTRADA[1], L. ANAYA ESPARZA[4], G. CAMARGO HERNÁNDEZ[5], L. HERNANDEZ[6];
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Abstract: *Caenorhabditis elegans* (*C. elegans*), one of the simplest organisms with a nervous system that performs many functions similar to those of the nervous systems of more complex organisms, is often studied as a model to help understand the basic mechanisms underlying complex behaviors. In particular, it possesses components of the serotonergic and dopaminergic systems present in vertebrates and its activity can be studied through stereotypic behaviors such as oviposition, which is directly linked to these neurotransmitters. On the other hand, *C. elegans* possess the same cellular and molecular mechanisms of response to oxidative stress seen in humans. The aim of this study was: To examine ovoposition behavior as an indirect indicator of serotonergic and dopaminergic activity in *C. elegans*, since these neurotransmitter systems are linked to this stereotypic behavior. Results: It has been reported that exogenous administration of dopamine inhibits ovoposition and exogenous serotonin stimulates this same behavior in *C. elegans*. In our study in agreement with the above, we found that 100 µM dopamine significantly reduced ovoposition to one third of that observed in control animals. Also in agreement with previous study, we found that 10 µM exogenous serotonin significantly increases ovoposition by about 30% relative to the control. We also observed the effect that H_2O_2-induced oxidative damage has on ovoposition, with H_2O_2 0.5 mM significantly reducing ovoposition by about 80% relative to the control. Conclusions: H_2O_2-induced oxidative damage mainly affects the serotonergic neurotransmitter system involved in the oviposition behavior of the nematode *C. elegans*.

Disclosures: L. Ramirez Contreras: None. **D. Aguilar Ocampo:** None. **M. Reveles González:** None. **M. Macías-Carballo:** None. **S. Sanchez:** None. **S. Hernández Estrada:** None. **L. Anaya Esparza:** None. **G. Camargo Hernández:** None. **L. Hernandez:** None.

Poster

PSTR333: Cellular Stress and Degeneration

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Program #/Poster #: PSTR333.27/C93

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01MH109382

Title: Analysis of Eif2ak3 alternative splicing as a potential regulator of PERK function in response to ER stress.

Authors: *E. ALVAREZ PERIEL[1], A. SINGH[2], K. L. JORDAN-SCIUTTO[1];
[1]Oral Med., Univ. of Pennsylvania, Philadelphia, PA; [2]Col. of Arts and Sci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: PERK, one of four integrated stress kinases that downregulate global translation by phosphorylating eukaryotic imitation factor 2 alpha, is responsible for sensing ER stress as part of the unfolded protein response and reestablishing cellular homeostasis, particularly proteostasis. Accordingly, its dysregulation has been associated to multiple pathological

contexts, particularly neurodegenerative disorders. PERK activity is regulated by phosphorylation, dimerization, protein stability and protein:protein interaction; however, little is known about regulation of *EIF2AK3*, the PERK coding gene and its RNA product, even though several *EIF2AK3* genetic variants have been associated with neuropathologic conditions. We have found that PERK mRNA levels are increased in astrocytes in response to ER stress. Moreover, the Ensembl database includes multiple *EIF2AK3* transcript variants, particularly in humans, suggesting that alternative splicing might be an additional regulatory mechanism for PERK. Thus, we investigated alternative *EIF2AK3* transcripts in mouse and rat primary neurons. Our results revealed expression of three previously unknown *EIF2AK3* variants in rat neuronal cultures, two of which can also be found in mouse primary neurons. In all cases, the alternative transcripts are predicted to lead to the activation of the nonsense-mediated decay pathway due to the presence of premature stop codons. Finally, levels of the *EIF2AK3* alternative splice variants increase in response to ER stress induction, suggesting their potential role in PERK regulation in this context. These findings suggest that additional mechanisms of PERK regulation may include alternative splicing and nonsense-mediated decay in neurons and possibly other cell types of the CNS.

Disclosures: E. Alvarez Periel: None. **A. Singh:** None. **K.L. Jordan-Sciutto:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.28/C94

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONAHCYT CF-G-597

Title: Elucidating the dose-response effect of the intraseptal injection of amyloid beta 25-35 peptide and the Cholino-protection of the recombinant C-terminal fragment of tetanus toxin.

Authors: *I. D. LIMON PEREZ DE LEON[1], A. PATRICIO-MARTÍNEZ[1,2], F. PATRICIO MARTÍNEZ[1,3], J. AGUILERA[4], F. SÁNCHEZ CANO[5];
[1]Lab. de Neurofarmacología, [2]Facultad de Ciencias Biológicas, [3]Facultad de Medicina Veterinaria y Zootecnia, Benemerita Univ. Autonoma De Puebla, Puebla, Mexico; [4]Inst. de Neurociències, Univ. Autònoma de Barcelona, Cerdanyola del Vallès (Barcelona), Spain; [5]CINVESTAV, Mexico, Mexico

Abstract: Amyloid beta protein (Aβ) and Aβ oligomers can trigger cascade neurotoxicity and neurodegeneration in Alzheimer's disease (AD). The toxic properties of the native full-length $Aβ_{(1-42)}$ peptide are retained in the 25-35 fraction of amyloid-β (Aβ25-35). However, the neurotoxic effects generated by the Aβ(25-35) peptide are more rapidly and cause more oxidative damage compared to those generated by Aβ(1-42). It has been shown that the non-toxic C-terminal fragment of tetanus toxin (Hc-TeTx) acts as a potent neuroprotector, preventing

neuronal death caused by apoptosis. The Hc-TeTx fragment corresponds to half of the heavy chain of tetanus toxin (TeTx) and is responsible for binding TeTx to the cell membrane and transporting the complete toxin retroaxonally to the CNS. This fragment is able to activate the neurotrophin receptors involved in the neural survival of cortical neurons, tropomyosin receptor kinases (Trks). Different studies have shown that the Hc-TeTx fragment exerts neuroprotective or restorative effects in animal models of neurodegeneration. The aim to is investigate the effects of three different concentrations of Aβ(25-35) in the medial septum (MS) of rats on spatial memory and nitrosative stress. After that most toxic concentration was obtained, and we evaluated the neuroprotective effect of the Hc-TeTx fragment on spatial memory and acetylcholinesterase (AChE) activity. Male rats of the Wistar strain were used, which were administered with different concentrations of Aβ(25-35) in the medial septum 100, 500, and 1 mM, respectively by stereotaxic surgery. The results show that the impairment of spatial memory in the group treated with Aβ25-35 was concentration-dependent, where the highest concentration of Aβ25-35 [1 mM] causes a significant impairment in spatial memory with respect to the control group. Meanwhile, [100μM] Aβ25-35 did not affect the spatial memory of rats. This effect is due to the fact that Aβ25-35 [1mM] increases the levels of NO and LPO, accompanied by greater immunoreactivity to 3-NT in MS and Hp. On the other hand, treatment with the Hc-TeTx fragment showed an improvement in spatial memory with respect to the SSI+Aβ25-35 group. AChE activity in the hippocampus decreases with respect to the SSI+Aβ25 group 35, while the Hc-TeTx+Aβ25-35 maintained AChE activity in SM compared to the intact group. In conclusion, these results indicate that Aβ25-35 causes nitrosative stress and impairment of spatial memory in a dose-dependent manner; on the other hand, it is suggested that intramuscular administration of the Hc-TeTx fragment has a protective effect on the cholinergic system.

Disclosures: I.D. Limon Perez De Leon: None. **A. Patricio-Martínez:** None. **F. Patricio Martínez:** None. **J. Aguilera:** None. **F. Sánchez Cano:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.29/C95

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: FJCU 112-A0112011

Title: Evaluating Resveratrol's Activation of AMPK-Dependent Pathways for Neuroprotection in 3D Human Neuronal Cells Against MPP+ Neurotoxicity

Authors: *M.-C. CHIANG[1], T. CHIANG[2], C. YEN[3];
[1]Fu Jen Catholic Univ., New Taipei City, Taiwan; [2]New Taipei Municipal Jinhe High Sch., Zhonghe Dist, Taiwan; [3]Ming Chuan Univ., Taipei, Taiwan

Abstract: Parkinson's disease (PD) is a debilitating neurodegenerative disorder characterized by dopaminergic neuronal loss and motor impairments. Oxidative stress and mitochondrial dysfunction contribute significantly to PD pathogenesis. This study investigated the neuroprotective potential of resveratrol, a natural polyphenol, against MPP+-induced neurotoxicity using SH-SY5Y cells cultured in a 3D cell culture system (e.g., scaffold) as a model. Resveratrol treatment significantly rescued cell viability, reduced caspase activity, and mitigated cytotoxicity induced by MPP+. Mechanistic studies revealed that Resveratrol activates AMPK-dependent pathways, upregulates anti-apoptotic gene expressions (Bcl-2), and promotes mitochondrial biogenesis (PGC1α, NRF1, Tfam). Furthermore, Resveratrol increased ATP levels, mitochondrial mass, and normalized oxidative stress. These findings collectively highlight Resveratrol's multifaceted neuroprotective effects, involving modulation of cellular energy metabolism, antioxidant defenses, and mitochondrial functions. Resveratrol holds promise as a therapeutic candidate for mitigating neurodegeneration in PD and related disorders through its actions on critical cellular pathways.

Disclosures: M. Chiang: None. **T. Chiang:** None. **C. Yen:** None.

Poster

PSTR333: Cellular Stress and Degeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR333.30/C96

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Lead toxicity. behavioral changes in a prenatally exposed mice model.

Authors: *A. MENDOZA MARTINEZ[1], F. PEREZ[2], E. GONZALEZ-GUEVARA[3]; [1]Neurofarmacología Mol. y Nanotecnología, Inst. Nacional Neurologia y Neurocirugia Manuel Velazco Suáez, Ciudad de Mexico, Mexico; [2]Neurofarmacología Mol. y Nanotecnología, Inst. Nacional de Neurología y Neurocirugía, Mexico, Mexico; [3]Neurofarmacología Mol. y Nanotecnología, Inst. Nacional de Neurología y Neurocirugía, Ciudad de Mexico, Mexico

Abstract: Lead toxicity: behavioral changes in a prenatally exposed mice model.Mendoza-Martínez A, Pérez-Severiano F. González-Guevara E.Lead is one of the most toxic elements that exist naturally then have persistent sources of exposure that cause environmental damage and health effects, lead exposure produces 900 thousand premature deaths and 800 thousand children suffer from lead poisoning. Mining and glazed earthenware are the main sources of lead exposure produced by environmental and occupational sources. No blood lead value is safe, Mexico maintains a value of 5 µg/dL as permissible limit. The population vulnerable to lead exposure are children and pregnant women, where the fetus is exposed through the mother. Exposure to lead presents irreversible health problems, influencing attention deficit, hyperactivity, and mainly behavioral problems.Aggressive behavior is regulated in part by serotonin (5-hydroxytryptamine). Serotonin interacts with 5-HT1A and 5-HT1B receptors to modulate aggressive behavior in animal species including humans. However, the possibility of

lead exposure to produce aggressive behavior and the molecular mechanisms in the serotonergic pathway that could be altered by exposure to Pb remain unclear. Therefore, in this study, a vulnerable population was analyzed, mice in the prenatal and postnatal stages, were exposed to 250 ppm of lead in beverage water and the aggressive behavior after 56 and 74 postnatal days was evaluated, using the resident intrusive behavior test, with parameters that indicate aggression. Significant differences were found, animals exposed to lead showed lower latency to attacks, a greater number of attacks and a longer duration of attacks. Animals exposed to Pb show a significant increase in aggressive behavior. Once that we observed that lead exposure induces aggressive behavior, the expression of the 5-HT1A and 5-HT1B receptors by western blot will be evaluated to determine the participation of serotoninergic pathway in aggressive behavior due to lead poisoning.

Disclosures: A. Mendoza Martinez: None. **F. Perez:** None. **E. Gonzalez-Guevara:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.01/C97

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant U54 NS127758-01

Title: Acute organophosphate intoxication in juvenile rats results in the development of spontaneous recurrent seizures & altered cognition

Authors: *I. M. G. TRIANA[1,2], M. A. MUNOZ[3], B. LE[1,2], P. J. LEIN[4], G. G. GURKOFF[5,2], A. IZADI[1,2];
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Abstract: Organophosphates (OPs) are potent cholinesterase inhibitors that were developed as industrial pesticides and repurposed as chemical weapons. In adult rats, acute intoxication with OPs can cause status epilepticus (SE) and lead to the development of spontaneous recurrent seizures (SRS), cognitive dysfunction, and persistent neurodegeneration and neuroinflammation. There are limited studies of the early outcomes following intoxication in juvenile rats but no long-term data. We hypothesize that acute intoxication with the OP diisopropyl fluorophosphate (DFP) will result in acute SE and the development of SRS, cognitive dysfunction, and persistent neurodegeneration in juvenile rats. Postnatal day (PND) 23, male Sprague Dawley rats were surgically implanted with electrodes in the dorsal hippocampus or received no implant (naïve). On PND 28, implanted rats were injected with DFP (3.75 mg/kg, s.c.) or an equal volume (300 µl) of vehicle (VEH, PBS, s.c.) followed 1 min post by atropine sulfate (0.1 mg/kg, i.m.) and 2-

pralidoxime (25 mg/kg, i.m.). Naïve animals received no treatment. Animals were recorded (LFP+video) for 21 days post-intoxication (PI). Six weeks PI, a subset of male rats were tested on the Barnes Maze (BM) and novel object recognition (NOR) tasks. Three months PI, animals were anesthetized with isoflurane, perfused with PBS, and brain tissue was collected for analyses. Tissue was stained with FluoroJade-C (FJC) for neurodegeneration. Images were acquired at 20X magnification using a high-content ImageXpress XL imaging system and analyzed with ImageJ. 44% of the animals developed SRS in 5.3 ± 0.7 days on average. While SRS frequency decreased on days 16-21, seizure duration significantly increased over the same period ($p<0.05$ Wilcoxon Signed Rank Test, n=6). There was a trend towards increased latency to find the escape box on the Barnes Maze compared to controls; on the NOR, epileptic rats did not indicate a preference between novel and familiar objects (BM and NOR: n=4 VEH, n=4 DFP). FJC staining of brains suggested no significant differences between groups in the number of positive FJC cell counts in the piriform cortex or dentate gyrus regions 3 months post-intoxication ($P > 0.05$, one-way ANOVA, n = 4 naïve, n = 4 VEH, n = 3 DFP). In addition to increasing the sample size for behavior, neuronal loss (NeuN) and neuroinflammation are additional critical outcomes that will be evaluated. Our data illustrate a similar pattern of chronic effects observed in juveniles as compared to adult rats following DFP intoxication, but a larger sample size, as well as chronic seizure monitoring, are needed to determine whether outcomes are as severe.

Disclosures: I.M.G. Triana: None. **M.A. Munoz:** None. **B. Le:** None. **P.J. Lein:** None. **G.G. Gurkoff:** None. **A. Izadi:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.02/C98

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DePaul University URC 602206

Title: Effects of early life environmental contaminant exposure on hypothalamic cFos responses to acute alcohol challenge in adolescence

Authors: G. M. VALDEZ[1], D. ROSS[2], C. E. DRESSEL[1], *M. R. BELL[1];
[1]Biol. Sci., [2]Hlth. Sci., DePaul Univ., Chicago, IL

Abstract: Polychlorinated biphenyls (PCBs) are ubiquitous and persistent environmental contaminants that were used in industry until their ban in the 1970s. While effects of PCBs on specific processes like endothelial inflammation, dopaminergic signaling, and neural dendritic organization are well-described, research is just beginning to understand how effects of PCBs may interact with other environmental challenges. For example, perinatal exposure to PCBs alters responses to an experimental inflammatory challenge (lipopolysaccharide). However, it is

unknown if this effect extends to other more human-relevant experiences. Acute alcohol intake activates dopaminergic and neuroimmune systems, serving as a useful model. We hypothesize that early-life PCB exposure may alter neural responses to acute alcohol exposure during adolescence, a period often marked by novel and excessive alcohol consumption. We focus on the paraventricular nucleus of the hypothalamus (PVN) because of its role in stress regulation and responses to acute alcohol. To study this, Sprague-Dawley dams were fed mixtures of PCBs (20 ug/kg BW, 1:1:1 Aroclor 1242, 1248, 1254) or oil vehicle on wafers throughout gestation. Adolescent offspring were given either ethanol (5 mg/kg BW) or a water gavage one hour before transcardial saline perfusion. The immediate early gene cFOS expression was quantified as an initial assessment of overall changes in neural activity. To do so, a hemi-section of brain was fixed and sectioned at 30 um. Sections were labeled with anti cFOS (1:2000, 24 hours, SySy Cat No. 226 308) and mounted with DAPI media. Fos positive (+) and negative DAPI-labeled nuclei were counted in three sections of PVN (Bregma: -1.40, -1.80, -2.12) per animal and averaged. Number and percentage of Fos+ nuclei were analyzed with a three way ANOVA (Sex x PCB x Ethanol), preliminary n = 7-8. As expected, animals challenged with ethanol showed a greater percentage of Fos+ cells compared to water controls ($F(1, 54) = 20$, $p < 0.01$). A main effect of PCB was detected, however it was qualified by interactions with other variables. Specifically, PCB exposure blocked the effect of ethanol in males but not in females ($F(1, 54) = 5.2$, $p < 0.05$). Consistent results were detected in the number of Fos+ cells. Earlier analysis of the central amygdala and prefrontal cortex did not reveal any effects of PCBs on Fos responses to ethanol. This indicates that the hypothalamus may be uniquely sensitive and could direct focus to critical cell populations. These results highlight the potential for long-lasting effects of PCBs on responses to environmental challenges, especially in adolescence.

Disclosures: G.M. Valdez: None. **D. Ross:** None. **C.E. Dressel:** None. **M.R. Bell:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.03/C99

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: AHW
NRC
R01
R35

Title: Single Cell RNA Sequencing Analysis of Alcohol Exposure's Impact on Neurodegenerative Pathology in Human Brain Organoids: Insights into Cell Type-Specific Mechanisms

Authors: *B. E. SCHULTZ[1], Y. YAN[1], T. ARZUA[1], X. BAI[2];
[1]Med. Col. of Wisconsin, Milwaukee, WI; [2]Cell Biol., Med. Col. of Wisconsin, MILWAUKEE, WI

Abstract: Alcohol use is a pervasive global health concern, with more than 220 million individuals aged 12 and older reporting alcohol consumption. Harmful use is known to cause cognitive impairments and behavioral issues such as depression, yet the underlying mechanisms remain elusive. This study used human induced pluripotent stem cell (iPSC)-derived cerebral organoids to investigate the cellular and molecular alterations underlying alcohol-induced brain pathology. We subjected two-month-old iPSC-derived cerebral organoids to various alcohol concentrations for six hours to mimic binge drinking. The expression of neuronal and astrocytic markers, beta Tubulin III and S100 respectively, facilitated cell type identification. Apoptosis was assessed using TUNEL staining, and cell-specific responses were analyzed via single-cell RNA sequencing (scRNA-seq) utilizing 10x Genomics technology. Our analysis revealed that alcohol exposure induced dose-dependent apoptosis in organoids, particularly affecting neuronal cells more than astrocytes. Moreover, differential gene expression analysis highlighted significant dysregulation in 505 genes in neurons, 472 genes in GABAergic neurons, and 421 genes in microglia. The dysregulated genes include AASS and ADAM19 in neurons, CACNA1A and MAPT in GABA neurons, and ADORA3 and ANXA2 in microglia. Bioinformatics analysis implicated the importance of dysregulated genes in neural development, axonal morphology, and inflammatory responses. Shared top dysregulated pathways across all these types involved organismal injury and abnormalities, indicating a commonality in the alcohol-induced response. Notably, mitochondrial gene expression in neurons also exhibited significant dysregulation, suggesting a mitochondrial component to the neurodegeneration observed in alcohol-exposed organoids. In conclusion, the study demonstrates the utility of cerebral organoids in modeling complex human brain disorders. The findings 1) underscore the profound adverse impact of alcohol on neuronal viability, and molecular and mitochondrial integrity within a controlled iPSC-derived human organoid model, 2) unveil comprehensive, cell type-specific responses to alcohol exposure, and 3) provide a valuable insight for future research into therapeutic strategies and drug development aimed at mitigating alcohol-induced neuronal damage through targeting brain cell type-specific molecular and mitochondrial signaling.

Disclosures: B.E. Schultz: None. **Y. Yan:** None. **T. Arzua:** None. **X. Bai:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.04/C100

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: AOD23007-001-00000; MOA-AI-21002-01

Title: Evaluating the long-term effects of sulfur mustard poisoning in rats

Authors: J. MORGAN, G. CAPACIO, M. PETTOVELLO, T. WHITTY, A. N. SANTORO, *H. MCCARREN;
US Army Med. Res. Inst. of Chem. Def. (USAMRICD), Aberdeen Proving Ground, MD

Abstract: Sulfur mustard (HD) is a cytotoxic blistering agent first used by the German army in WWI and is unique among chemical warfare agents in that it results in high rates of injury but low mortality. Dermal or vapor HD exposure results in acute injuries to the skin, eyes, and respiratory system, which have been widely reported. While the cytotoxic and vesicant properties of sulfur mustard are well documented, the mechanism of action is largely unknown, so there is no targeted therapy. In addition to acute injuries, HD exposure casualties from the Iran-Iraq war in the 1980's described CNS disturbances, such as confusion, lethargy, headache, impaired memory, sleep disturbances, and anxiety. It is unclear to what extent these symptoms can be linked to systemic HD toxicity versus the inherently traumatic experience of warfare. This suggests that HD may exert systemic toxicity that has been sparsely studied. This study endeavored to characterize the long term physiological and behavioral impacts of HD exposure in rats. Male and female Sprague Dawley rats were exposed subcutaneously to HD or ethanol (EtOH) and monitored for 14, 28, or 56 days post exposure for metrics of body weight, body temperature, and injury lesion, as well as behavioral metrics to include open field, elevated plus maze, sucrose preference test, and Barnes maze. Female rats exposed to EtOH travelled farther in the open field test than HD exposed females ($p=0.001$), however this dissipates in the 28-day ($p=0.75$) and the 56-day timepoints ($p=0.84$). A similar effect was seen in the Elevated Plus Maze, where EtOH exposed females in the 14-day group travelled greater distances then HD exposed females ($p=0.03$). Again - this effect was not seen in the 28 day and 56-day timepoints ($p=0.62$ and 0.76, respectively), suggesting that HD exposed females are less active and exploratory in the acute phase of HD poisoning. To that end, significant decreases in body temperature were seen in HD-exposed females when compared to the EtOH control animals in 13 of 15 measurements in the 14-day group (all p values <0.05). While neuropathology effects were not significant, the physiological and behavioral impacts seen in the 14-day female group suggest that there may be some systemic toxicity present, especially in this acute phase.

Disclosures: J. Morgan: None. **G. Capacio:** None. **M. Pettovello:** None. **T. whitty:** None. **A.N. Santoro:** None. **H. McCarren:** None.

Poster

PSTR334: Exposures and Neuroinflammation

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.05/C101

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Department of Defense (W81XWH-22-1-0749)

Title: Repopulating microglia following partial ablation promote cognitive function through alleviation of neuroinflammation in a mouse model of chronic Gulf War Illness

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Abstract: More than one-third of the 700,000 US military members who deployed in the first Gulf War display a variety of chronic, unexplained symptoms known as Gulf War Illness (GWI). Based on epidemiological evidence, GWI is most likely the consequence of exposure to nerve gas prophylactic medicine, pyridostigmine bromide, and pesticides such as permethrin. Chronic neuroinflammation has been identified as one of the primary pathological changes causing cognitive impairment in GWI. Previous studies on animal models exhibiting chronic neuroinflammation have demonstrated that a short-term pharmacological ablation of activated microglia with the small molecule PLX5622 can lead to the repopulation of microglia with homeostatic function, reducing neuroinflammation and improving cognitive function. We investigated whether transient ablation of microglia in chronic GWI would also alleviate cognitive impairments by reducing neuroinflammation. Ten days of exposure to pyridostigmine bromide and the insecticide permethrin resulted in long-term cognitive impairments in C57BL6 mice when tested 10 months post-exposure. A cohort of GWI mice displaying cognitive impairment received PLX5622 via diet for 28 days, which resulted in a 70% depletion of microglia in the cortex and 64% in the hippocampus. GWI mice continued to show impaired cognitive ability when assessed immediately after partial microglial ablation, apparent from loss of ability for object location memory formation, pattern separation, and temporal pattern processing, implying residual microglia were inadequate to alleviate cognitive dysfunction. Interestingly, PLX5622-treated GWI mice displayed better abilities for object location memory, pattern separation, and temporal pattern processing when examined 30 days after PLX5622 withdrawal, compared to age-matched GWI mice, implying that repopulated microglia following transient ablation have mediated beneficial effects. Microglial analyses in the hippocampus and cerebral cortex displayed reduced microgliosis and activation of microglia in GWI animals treated with PLX5622. In addition, in the hippocampus and the cortex, morphometric analysis revealed an abundance of microglia with highly ramifying processes, a characteristic of non-inflammatory microglia, compared to amoeboid microglia with fewer processes (inflammatory phenotype) in GWI mice. Moreover, reduced percentages of microglia displayed NLRP3 inflammasome complexes in GWI mice treated with PLX5622 than in GWI mice. Thus, spontaneous repopulation of microglia after their partial ablation mitigated neuroinflammation, which improved cognitive function in chronic GWI.

Disclosures: M. Kodali: None. **C. Jordan:** None. **C. Huard:** None. **Y. Somayaji:** None. **X. Rao:** None. **B. Shuai:** None. **A.K. Shetty:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.06/C102

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: This research is supported by the Department of Defense grant W81XWH-16-1-0586 to NMF.

Title: Delayed treatment with LNFPIII and/or dietary intervention with the prebiotic inulin shows sex-specific effects in a preclinical model of Gulf War Illness

Authors: *B. T. HUDSON, T. P. KALINOWSKI, J. J. WAGNER, N. M. FILIPOV;
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Abstract: Gulf War Illness (GWI) is a chronic, multisymptomatic illness, likely related to concomitant exposure to pesticides such as DEET, nerve agents such as sarin, the nerve agent prophylactic pyridostigmine bromide (PB), and wartime stress during the 1990-1991 Gulf War. Approximately 30% of veterans that served in this conflict have been diagnosed with GWI. It is of particular relevance that this conflict was also the first to see female US service members on the frontline. Past GWI research focused on investigating sex differences and potential therapeutic options in females is lacking. Thus, using an established preclinical GWI model, we investigated long-term behavioral effects of this disease in both male and female mice and assessed the efficacy of a delayed intervention with (1) a novel immunotherapeutic, Lacto-N-Fucopentaose III (LNFPIII), (2) dietary supplementation with the prebiotic inulin, or (3), the LNFPIII-inulin combination. To achieve these objectives, male and female C57BL6/J mice (8-9 weeks of age) were given PB and DEET for 14 days. Corticosterone was added to the drinking water in the latter 7 days to emulate wartime stress. On day 15, mice received a single dose of the sarin surrogate diisopropylfluorophosphate (DFP). Eight months following this, LNFPIII treatment and/or dietary intervention with inulin began. A month later, mice underwent a battery of behavioral tests, including the sucrose preference, coat state, nesting, elevated zero maze, marble burying, open field, grip strength, pole test, gait test, a 3-stage variation of the novel object test, sticker removal, forced swim, and Barnes maze tests in order to assess motor, mood, and cognitive function. The data that has been analyzed thus far show that GWI males, but not females, have significantly decreased maximal grip strength, which was not influenced by LNFPIII or dietary inulin. On the other hand, both maximal and average grip strength in all females on inulin-fortified diet was significantly higher. There were no significant effects of GWI treatment or delayed interventions in the pole test time to finish for males. In contrast, GWI females tended to be slower in pole test time to finish and, notably, female mice that received both LNFPIII and inulin were faster irrespective or GWI status. Mice from both sexes exhibited strong sucrose preference that was unaffected by GWI treatment, LNFPIII, or inulin in the diet. These data suggest that motor function may be impaired by earlier, GWI-related, chemical exposure in both sexes, but in different domains; also, females specifically may be particularly sensitive to the beneficial effects of inulin and LNFPIII in improving motor performance.

Disclosures: B.T. Hudson: None. **T.P. Kalinowski:** None. **J.J. Wagner:** None. **N.M. Filipov:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.07/C103

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: (AOD24006-001 00000) between the NIH OD and the USAMRICD under the oversight of the CCRP within the OBRS at the NIAID/NIH

Title: Age differences in organophosphorus nerve agent-induced toxicity, epileptogenesis, blood brain barrier integrity and neurodegeneration in rats treated with midazolam

Authors: C. R. SCHULTZ[1], D. A. NGUYEN[1], J. NIQUET[2], M. F. STONE[1], B. MARRERO-ROSADO[1], M. DE ARAUJO FURTADO[3], A. K. BINEY[1], *L. A. LUMLEY[1]; [1]USAMRICD, Aberdeen Proving Ground, MD; [2]UCLA-VAMC, Los Angeles, CA; [3]BioSEaD, Rockville, MD

Abstract: Exposure to organophosphorous nerve agents (OPNAs) irreversibly inhibits acetylcholinesterase and may lead to cholinergic crisis and seizure. Although benzodiazepines are the standard of care after OPNA-induced status epilepticus, when treatment is delayed for up to 30 min or more, refractory status epilepticus can develop. The predominant focus in preclinical research has been on the therapeutic evaluation of adult male rodent models, potentially overlooking a diverse response across a heterogenous population characterized by differences in age, sex, and health status. Although there may be age and sex differences in toxicity from OPNA exposure or response to medical countermeasures, a majority of research assessing therapeutic efficacy has been conducted in adult male animals. Consequently, we evaluated the age and sex differences of soman-induced toxicity, epileptogenesis, and neurodegeneration in OPNA-exposed rats treated with midazolam. We previously reported that juvenile rats are less susceptible to the lethal effects of the OPNA soman compared to adults, while pups are the most susceptible. Currently we report on the age and sex differences in the delayed midazolam treatment on survival, seizure and brain pathology in soman exposed rats. Male and female pups (postnatal day [PND]14), juveniles (PND42), and adult (PND70) rats were challenged with an equitoxic dose of soman and then treated with an admix of the muscarinic antagonist atropine sulfate and the oxime HI-6 1 min after exposure, followed by midazolam 40 min after seizure onset. Survival as well as seizure data including spontaneous recurrent seizure were evaluated. Brains were processed to assess neurodegeneration, neuroinflammation, blood brain barrier (BBB) integrity, and peripheral immune cell infiltration. Midazolam-treated adult rats had better survivability compared to the juveniles and pups. However, lethality in young rats occurred prior to the administration of midazolam, suggesting that young rats have a narrower window of treatment time. In juvenile and adult rats, midazolam did not prevent soman-induced BBB disruption, epileptogenesis, neurodegeneration, microglial activation, and astrogliosis, while in general brains of surviving pups were not damaged. Despite a higher survivability, adult rats had poorer neuropathological outcomes and increased proportion of epileptogenesis compared to juvenile rats, with minimal sex differences. In conclusion, adjunct therapies to midazolam are needed and it is important to evaluate age and sex as factors in therapeutic response.

Disclosures: C.R. Schultz: None. **D.A. Nguyen:** None. **J. Niquet:** None. **M.F. Stone:** None. **B. Marrero-Rosado:** None. **M. de Araujo Furtado:** None. **A.K. Biney:** None. **L.A. Lumley:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.08/C104

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Embelin Modulates p38 MAPK Signaling Pathway and Neurotransmitter Levels in Ethidium Bromide-Induced Multiple Sclerosis Rat Model

Authors: *R. ARORA;
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Abstract: Embelin Modulates p38 MAPK Signaling Pathway and Neurotransmitter Levels in Ethidium Bromide-Induced Multiple Sclerosis Rat ModelRimpi AroraDepartment of Neurology, Christian Medical College and Hospital, Ludhiana, India
Background: Multiple sclerosis (MS) is characterized by demyelination and neuroinflammation, with the p38 mitogen-activated protein kinase (MAPK) pathway playing a pivotal role. Embelin (EMB), derived from Embelia ribes, exhibits anti-inflammatory properties.**Objective:** This study aimed to explore EMB's neuroprotective effects in ethidium bromide (EB)-induced MS model in rats, focusing on the modulation of the p38 MAPK signaling pathway.**Methods:** Wistar rats were divided into groups and administered EB to induce MS-like manifestations. EMB was administered at varying doses. Neuroinflammatory cytokines (TNF-α, IL-1β, IL-6) and neurotransmitter levels (GABA, DA, 5-HT, glutamate) were analyzed.**Results:** EMB effectively reduced neuroinflammatory cytokines and modulated neurotransmitter levels, enhancing GABA, DA, and 5-HT while reducing glutamate in EB-treated groups.**Conclusion:** EMB demonstrates promise as a therapeutic agent for MS, potentially acting through the modulation of the p38 MAPK signaling pathway, and merits further investigation.**Keywords:** Multiple sclerosis (MS); Embelin; p38 MAPK signaling; Neuroinflammation; Neurotransmitters.

Disclosures: R. Arora: None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.09/C105

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: The influence of quercetin on the toxic effect of excessive manganese (experimental rat model)

Authors: *M. MIKADZE[1], T. BIKASHVILI[2];
[1]Ivane Beritashvili Ctr. of Exptl. Biomedicine, Tbilisi, Georgia; [2]Neurotoxicology, Ivane Beritashvili Ctr. of Exptl. Biomedicine, Tbilisi, Georgia

Abstract: Manganese (Mn) is an essential trace element, but overexposure to Mn has been associated with neurotoxicity. In this work neuroprotective effect of quercetin was investigated. Four-week-old wistar rats with body weight between 80-120 g were studied, they were assigned to groups: rats in control groups (male, female) were given regular water, while rats in other groups drank water with final manganese concentration of 20 mg/ml (male, female) and manganese with quercetin (25 mg/kg) for three months. To study exploratory and anxiety behavior rats were tested in open field and elevated plus maze. To estimate learning and memory status a multibranched maze was used. Intoxication with manganese compounds had a significant impact on the emotional state of animals. The behavioural disturbance of male rats was more noticeable than that of female rats in the same group. It was revelaed that manganese poisoning increased Mn contents in the brain of both genders, caused slight damage of neurons and produced notable gliosis. The excess amount of manganese in the brain had a strong impact on learning processes. Decreased locomotor activity was observed in female rats. Disorders in the learning process were more pronounced in male individuals. The Exposure to quercetin had positive effects on the impairments caused by manganese intoxication, especially on the learning process. The number of errors of male rats of the manganese/quercetin group equaled the same number of the control group. In female rats, the impairment caused by manganese intoxication was expressed in the rate of time required to pass the maze and in this case the quercetin group had almost the same rate of errors such as control group rats. Accumulation of manganese ions from areas of the brain is particularly pronounced in the hippocampus and cerebral cortex. Decreased number of neurons was statistically significant in CA3 and dentate gyrus regions. In the quercetin/manganese group rats the number of neurons in these regions remained close to the number of neurons of control groups.

Disclosures: M. Mikadze: None. **T. Bikashvili:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.10/C106

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Effect of Arsenic on rat learning ability and brain neuroarchitecture

Authors: *T. BIKASHVILI[1], M. MIKADZE[2];
[1]Ivane Beritashvili Ctr. of Exptl. Biomedicine, Tbilisi, Georgia; [2]Neurotoxicology, Ivane Beritashvili Ctr. of Exptl. Biomedicine, Tbilisi, Georgia

Abstract: Arsenic (As) is a naturally occurring element, ubiquitous in the environment in both organic and inorganic forms. Inorganic As, the more toxic form, is found in groundwater, surface water and food. Brain is a soft target for As toxicity as it freely crosses blood-brain barrier. Our research objective was to study the effect of As exposure on the learning process and brain morphology of the young and adult rats. All experiments were performed using male Wistar rats of two different age groups (young P28-30 and adult P60-65 at the start of experiments). Rats in control groups drank regular water, and rats in experimental groups got water containing As at concentration 68 mg/L for 3 months. The process of learning was estimated by maze test performance (to reach the nest box) within 5 min by number of errors made during ambulation through the maze (enter into the blind alley section) and by the time of maze passage. The results of multi-branched maze performance showed that arsenic exposed young animals need the same time to learn the correct maze performance as the control ones. There was no difference in errors made either. The process of learning in this maze was considerably difficult in the adult arsenic exposed group. They need more time and made more errors for passing the maze compare the control rats. Dendritic spines mediate most excitatory connections in the central nervous system, and are now regarded as key elements in neuronal circuitry. Structural plasticity of hippocampal spines provides the basis for synaptic efficacy underlying learning and memory processes. The results obtained in our experiments showed that dendritic spine density and proportion of thin, stubby and mushroom-shaped were affected. As exposure induces structural changes in the dendritic spine morphology in the hippocampal neurons, which could alter synaptic efficacy and impede the learning and memory processes.

Disclosures: T. Bikashvili: None. **M. Mikadze:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.11/C107

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: The effects of methanolic extract of Syzygium guineese (Myrtaceae) wild D.C on lead-induced neurotoxicity in the prefrontal cortex of Wistar rats

Authors: *S. K. LAWAL[1], S. O. OLOJEDE[2], K. S. DITHOLE[1], O. O. AZU[3], T. T. MAMALELALA[1], V. O. MAKANJUOLA[4];
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Abstract: Backgrounds: Antimicrobial and wound-healing activities of *Syzygium guineense* have been extensively documented, but its use in managing lead-induced neurotoxicity remains less explored. Hence, this study is aimed at examining the effects of *Syzygium guineense* leaf (SGL) extract on lead-induced prefrontal cortex (PFC) damage in Sprague-Dawley rats using histological and biochemical indices. **Method:** Twenty-five Wistar rats (60 - 80 g) were assigned into five groups (n=5). Group 1 (distilled water 1 ml/kg); Group 2: (Lead, 5mg/kg); Group 3: (Lead 5mg/kg + SGL, extract, 100 mg/kg); Group 4: (Lead, 5 mg/kg + SGL extract 250 mg/kg); Group 5: (lead, 5mg/kg + SGL extract 400 mg/kg). PFC was excised for histological (using haematoxylin & eosin and cresyl fast violet stains) and biochemical (Malondialdehyde MDA, Glucose-6-phosphate dehydrogenase G6PDH and Lactate dehydrogenase LDH) analyses after two weeks of treatment. **Results:** There was a significant increase ($P<0.05$) in PFC-MDA level in the rat administered with a lead-only compared with SGL extract treated groups and control. Between the rats that received lead-only and SGL-treated groups, there was a significant difference ($P<0.05$) in G6PDH level but no significant difference ($P>0.05$) in LDH level. The lead-treated group only and a low dose of SGL extract showed PFC pyknotic neuronal cells. Notably, there was an improved PFC histo-architecture and Nissl staining outcome in the groups treated with 400 mg/kg b.wt. of SGL extract. **Conclusion**: This study suggests that *S guineense* leaf extract at higher doses can potentially ameliorate the effects of lead-induced prefrontal cortex damage.

Disclosures: S.K. Lawal: None. **S.O. Olojede:** None. **K.S. Dithole:** None. **O.O. Azu:** None. **T.T. Mamalelala:** None. **V.O. Makanjuola:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.12/C108

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NATO-Science for peace and security programme: SPS G5852

Title: N-acetylcysteine-amide (AD4) protects against oxidative stress, neuroinflammation and memory impairment in a survival mouse model of acute paraoxon intoxication.

Authors: *E. URQUIZU LLOP[1,2], M. CUILLER[1], D. RALDUA[3], D. Z. ATLAS[4], M. H. BUENROSTRO-JAUREGUI[5], D. PUBILL[1], J. CAMARASA[1], E. ESCUBEDO[1], R. LÓPEZ-ARNAU[1];
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Abstract: Organophosphorus compounds are widely used as pesticides in agriculture and employed as nerve agents in chemical war and terrorist activities. Indeed, their neurotoxic activity, due to acetylcholinesterase inhibition, can cause great hazard to human health. Among these compounds figures paraoxon-ethyl (POX), whose exposure may produce organophosphorus poisoning (OPP), characterized by cholinergic syndrome thus leading to neurodegeneration and brain damage. Despite the risk of intoxication, the standard therapy has not changed over the last decades and does not target secondary toxicity. Therefore, the aim of this study was to test the therapeutic potential of N-acetylcysteine-amide (AD4), a blood brain barrier permeable peptide to protect against acute OPP in a mouse survival model of acute POX intoxication. Swiss CD-1 male mice were injected subcutaneously (s.c.) with POX at a dose of 4 mg/kg, followed by an intraperitoneal (i.p.) injection of atropine sulphate (4 mg/kg) and pralidoxime chloride (2-PAM) (25 mg/kg) one minute later. One hour later, diazepam (5 mg/kg, i.p.) and 2-PAM were injected to control and terminate seizures. Moreover, another group of mice were also administered AD4 (150 mg/kg, i.p.) 2 and 6 hours after POX administration. Nine to eleven days after treatment, Novel Object Recognition Test (NORT) was performed to determine possible memory impairments. Furthermore, 72h after POX administration, mouse brain hippocampus (hp) were dissected out to study oxidative stress markers (4-Hydroxynonenal (4-HNE) and Glutathione Peroxidase 1 (GPx1) protein levels) by following a kit and a general western blotting procedure. Moreover, neuroinflammation was determined by glial fibrillary acidic protein (GFAP) immunostaining. Results demonstrated that treatment with AD4 in the POX survival mouse model partially rescued cognitive decline measured via NORT ($n=13$, $p< 0,001$). Regarding oxidative stress, AD4 treatment prevents the increase of 4-HNE levels induced by POX acute intoxication in hp ($n=7$, $p<0,001$). Moreover, AD4 treatment also reverted the decrease in GPx1 protein levels induced by POX intoxication ($n=7$, $p<0,001$). Regarding neuroinflamation, AD4 treatment significantly attenuates the increase of GFAP levels induced by acute POX intoxication in both the dentate gyrus and CA3 areas of the hp ($n=5-7$, $p<0,05$). However, AD4 treatment had no effect in the CA1 area of the hp. In conclusion, this study suggests that AD4 may possess potential therapeutic effects to counteract the secondary neurotoxicity (oxidative stress, neuroinflamation and memory impairments) generated by acute OPP.

Disclosures: E. Urquizu Llop: None. **M. Cuiller:** None. **D. Raldua:** None. **D.Z. Atlas:** None. **M.H. Buenrostro-jauregui:** None. **D. Pubill:** None. **J. Camarasa:** None. **E. Escubedo:** None. **R. López-Arnau:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.13/C109

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Orally administered microplastics affect the cytoarchitecture of the dentate gyrus in mice.

Authors: *T.-Y. HE[1], L.-J. LEE[2];
[1]Grad. Inst. of Anat. and Cell Biol., [2]Anat. and Cell Biol., Natl. Taiwan Univ. Col. of Med., Taipei, Taiwan

Abstract: Plastic pollution aroused global concern in recent years. Microplastics (MPs), degraded from plastic products, are released into the water, air, soil, and sediment and then consumed by humans through the food chain. Although plastic particles have been detected in human feces, placenta, and blood, the influences of MPs on brain health are still largely unknown. In this aging society, it is also necessary to pinpoint the impact of MPs on the aged brain. In this study, 5 μm MPs of low (7 mg/kg) and high (15 mg/kg) concentrations or saline were orally administered to 14-month-old C57BL/6J male mice twice a week for one month. The dendritic structures of granule cells in the dentate gyrus revealed by the Golgi stain were characterized. MPs of both low and high concentrations reduced the dendritic complexity and length but not the spine density. Importantly, cotreatment of an antibiotic cocktail (0.5 g/L ampicillin, 1 g/L neomycin, 1 g/L metronidazole, and 0.25 g/L vancomycin) in drinking water rescued the dendritic changes induced by MPs. Our study demonstrated the impact of microplastics on dendritic features and the therapeutic potential of an antibiotic cocktail, suggesting the role of neuroinflammation following chronic exposure to microplastics.

Disclosures: T. He: None. **L. Lee:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.14/C110

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DGAPA-UNAM (PAPIIT IN204324)

Title: Study on the accumulation of alpha-synuclein in Wistar rats exposed to ozone pollution

Authors: M. VALDES-FUENTES[1], A. E. RODRIGUEZ[2], *S. RIVAS-ARANCIBIA[3];
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Abstract: Environmental pollution, mainly ozone (O_3), contributes to the generation of reactive oxygen species in the body, which allows the generation of a state of oxidative stress causing various chronic non-infectious diseases, such as neurodegenerative diseases. On the other hand, it is known that various cellular and molecular mechanisms link the loss of intestinal permeability and the subsequent generation of some neurodegenerative diseases. Studying some proteins involved in the communication between the immune system and the establishment of pathology allows us to know key pieces to understand the regulatory mechanisms. The protein alpha-synuclein (a-Syn) and its misfolding have been associated with important pathologies such

as Parkinson's disease. Furthermore, critical components for the proinflammatory response, such as the transcription factor NFκB and interleukins such as IL-17, play an important role in regulating homeostasis and its pathophysiology. This study aims to establish bases that allow us to know the relationship between chronic exposure to low doses of ozone, the immune response, and the establishment of proteins that are part of the generation of neurodegenerative diseases. For this study, 72 Wistar rats were used, which were divided into 6 random groups that received the following treatments: 1) Control (exposed to air); 2) O_3 7 days; 3) O_3 15 days; 4) O_3 30 days; (5) O_3 60 days and (6) O_3 90 days. After completing the treatment, the animals were deeply anesthetized, and death and the tissues were extracted and processed for Western Blot, immunohistochemistry, and qPCR techniques. The results indicate a significant increase in a-Syn protein in SN from 7 to 60 days of exposure, similar to what was observed in the jejunum. The NFkB protein has a significant increase at 7 days in the *substantia nigra*, while in the jejunum, a significant increase is observed at 7 and 15 days and a decrease at 60 and 90 days for the colon. Interleukin IL-17 shows an increase at 90 days in the *substantia nigra*, while for the jejunum, there is an increase at 30 days, and for the colon, at 15 and 90 days. These results show us that, during a state of oxidative stress induced by chronic exposure to ozone, there is an a-Syn increase in the presence of the protein, which allows the generation of loss of regulation of the inflammatory response, contributing significantly. to the establishment of neurodegenerative diseases. Grant: DGAPA-UNAM (PAPIIT IN204324) to S.R-A.

Disclosures: M. Valdes-Fuentes: None. **A.E. Rodriguez:** None. **S. Rivas-Arancibia:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.15/C111

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Proyecto Conacyt Doctorados No. 259542 Fondo 1.1.4.8.4
PROSNI 2021; 259639
PROSNI 2022; 265178.
beca CONACYT; 882378

Title: Neuroprotecteffect of curcumin on the activation of Nrf2 in the hippocampus of rats exposed to ozone and on the activity of antioxidant enzymes in plasma.

Authors: *A. A. M. RAMIREZ MENDOZA[1,2], M. A. RAMIREZ-HERRERA[3], M. L. MENDOZA-MAGANA[4], M. E. URENA-GUERRERO[6], J. CASTAÑEDA-CABRAL[5];
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Abstract: Ozone (O_3) is a tropospheric pollutant that causes oxidative damage to biological substrates through the formation of reactive oxygen, and nitrogen species (RONS). When oxidative damage is severe and prolonged the endogenous antioxidant system, regulated by Nrf2, is depleted leading to decreased activity of antioxidant enzymes such as catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD). Curcumin (CUR) is a natural polyphenol with well-documented antioxidant and anti-inflammatory properties, which modulates transcription factors such as Nrf2. The aim of this study was to evaluate the effects of CUR on Nrf2 activation level, as well as on the activity of CAT, GPx, and SOD after acute and chronic exposure to O_3. Fifty male Wistar rats were divided into 5 experimental groups: intact control, CUR-fed control, O_3-exposed control, CUR-fed preventive/O_3-exposed, and CUR-fed therapeutic/O_3-exposed groups. The latter two groups received a dietary supplementation with CUR while being exposed to O_3. These experiments were conducted during acute and chronic exposure phases. In the preventive and therapeutic groups, the effect of CUR on Nrf2 activation levels maintained it in a functional state, while the activity of CAT, GPx, and SOD in plasma increased in both exposure phases with slight differences. Therefore, we propose that CUR could act to stabilize Nrf2 activation level to achieve optimal activity of antioxidant enzymes, leading to a decrease in oxidative damage caused by O_3 exposure.

Disclosures: A.A.M. Ramirez Mendoza: None. **M.A. Ramirez-Herrera:** None. **M.L. Mendoza-Magana:** None. **M.E. Urena-Guerrero:** None. **J. Castañeda-Cabral:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.16/C112

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: A multiscale ecological neuroscience approach to identifying and eliminating neurotoxins in urban and workplace environments

Authors: *E. OHAYON[1,2], C. LAINSCSEK[3], J. L. OHAYON[4];
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Abstract: There is an increasing recognition that the narrow and pervasive focus on molecular events is limiting our understanding of embodied brain activity and cognition. Moreover, these deficiencies in brain and health modeling obstruct the ability to assess and mitigate disease and other adverse conditions. A central challenge is the scarcity of scientific approaches that can

integrate across scales. Here we outline how a work that began with considering multiscale neuro-inflammatory processes in COVID-19 and Alzheimer's Disease and Related Dementias (ADRD) can be extended well beyond traditional Adverse Outcome Pathway (AOP) approaches. In particular, we apply a novel multiscale ecological neuroscience approach to assess the causal pathway, impact and mitigation of neurotoxins commonly found in urban and workplace environments. Key aspects of the new approach include the evaluation of: [1] Multiscale factors (spatiotemporal) [2] Adverse as well as Advantageous outcomes [3] Recurrent Interacting Pathways and [4] assessment of impact in the form of Outcomes and Systems Analysis (a MAARIPOSA Framework). By expanding across scales, models can now encompass key events and their relationships ranging from the molecular (e.g., oxidative stress, neurotoxic elements), cellular (microglia proliferation, proinflammatory cells), systems (blood brain barrier disruption), individuals (psychological stress, agency, consciousness), social (disparities, discrimination, public health measures) and environmental (incursion, pollution, toxics, climate, regulations). As concreate examples, we examine the application of broadly used chemicals in urban landscaping (e.g., glyphosate-based herbicides) and fumigant insecticides (e.g., sulfuryl fluoride in termite control). We demonstrate how initiating events at the environmental and social levels can precede molecular events and that neurotoxic and other health impacts can be modeled even when the adverse molecular pathways are poorly understood. As such, the approach can help identify alternative practices and solutions that do not rely on molecular intervention (e.g., non-toxic alternatives, public education, regulatory practices). We further suggest how the methodology can be extended so that causal pathway strength might be computationally quantified based on existing epidemiological data, case studies and the known pathways of related conditions. A multiscale framework thus supports a "precautionary principle" approach with broad applications in workplaces, clinical settings and environmental health initiatives across organizational scales (e.g., local, municipal, federal).

Disclosures: E. Ohayon: None. **C. Lainscsek:** None. **J.L. Ohayon:** None.

Poster

PSTR334: Exposures and Neuroinflammation

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR334.17/C113

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R01NS088645
NIH R03AG064266

Title: A novel murine Tdp-43ΔNLS knock-in mouse model reveals impaired DNA double-strand break repair, neuroinflammation, and senescence

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Abstract: TDP-43 mislocalization and aggregation are key pathological features of motor neuron diseases (MND) including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). However, transgenic hTDP-43 WT or ΔNLS-overexpression animal models mainly capture late-stage TDP-43 proteinopathy, and do not provide a complete understanding of early motor neuron-specific pathology during pre-symptomatic phases. We have now addressed this shortcoming by generating a new endogenous knock-in (KI) mouse model using a combination of CRISPR/Cas9 and FLEX Cre-switch strategy for the conditional expression of a mislocalized Tdp-43ΔNLS variant of mouse Tdp-43. This variant is either expressed conditionally in whole mice or specifically in the motor neurons. The mice exhibit loss of nuclear Tdp-43 concomitant with its cytosolic accumulation and aggregation in targeted cells, leading to increased DNA double-strand breaks (DSBs), signs of inflammation and DNA damage-associated cellular senescence. Notably, unlike WT Tdp43 which functionally interacts with Xrcc4 and DNA Ligase 4, the key DSB repair proteins in the non-homologous end-joining (NHEJ) pathway, the Tdp-43ΔNLS mutant sequesters them into cytosolic aggregates, exacerbating neuronal damage in mice brain. The mutant mice also exhibit myogenic degeneration in limb muscles and distinct motor deficits, consistent with the characteristics of MND. Our findings reveal progressive degenerative mechanisms in motor neurons expressing endogenous Tdp-43ΔNLS mutant, independent of TDP-43 overexpression or other confounding etiological factors. Thus, this unique Tdp-43 KI mouse model, which displays key molecular and phenotypic features of Tdp-43 proteinopathy, offers a significant opportunity to further characterize the early-stage progression of MND and also opens avenues for developing DNA repair-targeted approaches for treating TDP-43 pathology-linked neurodegenerative diseases.

Disclosures: J. Mitra: None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.01/C114

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: UK MRC Grant MR/X032019/1

Title: Infection of human cortical organotypic brain slice cultures with Cryptococcus neoformans causes localized inflammation and death in host microglia

Authors: *A. DE LANGE[1], A. N. AWALA[2], M. B. VERHOOG[2], J. T. BUTLER[3], J. M. ENSLIN[4], A. G. FIEGGEN[2], J. V. RAIMONDO[2], R. DANGAREMBIZI[5];
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Abstract: Cryptococcal meningitis (CM) is a life-threatening fungal brain infection that is estimated to cause 181 000 deaths annually. However, the pathophysiology of CM remains

largely unknown. Human cortical organotypic brain slice cultures (HCOBSCs) present a recent advance in tissue culture which can be harnessed to study pathology in CM. This study aimed to determine how inflammation and cell death fluctuate in HCOBSCs over a two-week culture period and what proportion of inflammation and cell death occur in microglia. We further sought to measure inflammation and death in microglial cells in response to cryptococcal infection. To achieve these aims, 250 µm-thick sections were made from blocks of human cortical tissue acquired from patients undergoing medically necessary brain surgeries, and were cultured in a specialized growth medium. Slices were collected and fixed on predetermined days over a 14-day-period. On the 6th day of culturing, some slices were also treated with either 5 x 106 CFU of C. neoformans, 100 ng/ml of lipopolysaccharide (as a positive control for inflammation), or normal growth media, for 24 hours. Using immunofluorescent staining, we tracked the activation and nuclear translocation of nuclear factor for interleukin 6 (NF-IL6) as an indicator of inflammatory activation, we utilised propidium iodide staining as an indicator of cell death, and we used Iba1 as a microglia-specific marker. Our data from confocal imaging suggests that baseline NF-IL6 expression in HCOBSCs is highly variable between patients, but generally reduces after a few days. Total cell death peaks in the first two days in vitro, then stabilises. We further observed that NF-IL6 expression and propidium iodide staining in microglial cells is increased in areas where there is extensive infection of the brain tissue by cryptococcal cells, but that this increase is not generalised. We conclude that HCOBSCs can most effectively be used to study inflammation and cell death after several days in vitro, and that C. neoformans may exert different effects on microglial cells in close vicinity than on microglial cells distant from the sight of infection.

Disclosures: A. de Lange: None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.02/C115

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Tulane Brain Institute Pilot Award
NIGMS P20GM103629
NINDS RO1 grant: NS114286
NIA RO1 grant: AG074489
NIA RO1 grant: AG072676

Title: Repeat Infection With Cytomegalovirus Impacts Cognition and Neuroinflammation

Authors: *N. BARAHONA[1], S. MORRIS[1], S. R. WROBLEWSKI[2], K. ZWEZDARYK[1], E. B. ENGLER-CHIURAZZI[3];
[1]Tulane Univ., New Orleans, LA; [2]Tulane Univ. Grad. Neurosci. Program, New Orleans, LA; [3]Neurosurg., Tulane Univ., New Orleans, LA

Abstract: It is well established that acute infections can have negative effects on cognitive function and brain biology and that these impacts may intensify with age. Emerging evidence indicates that a greater lifetime exposure to infections can lead to decreased cognitive ability and an increased rate of cognitive decline, though contributions of cytomegalovirus (CMV) are unclear. Our aim was to evaluate the cognitive and histological consequences of intermittent CMV exposure across the lifespan to elucidate inflammatory mechanisms underlying cognitive and brain aging. We hypothesized that increasing CMV exposures would contribute to an increased severity of cognitive impairment and neurological defects. Eight-week-old female BALB/c mice were initially exposed to either a CMV (Smith strain, $1x10^5$ PFU) or a mock (murine salivary gland extract in PBS) virus via intraperitoneal injections. Viral latency was achieved after 14 days, and the virus (either CMV or mock) was readministered every 13 weeks until tissue collection at ~3, 8, 14, or 20 months of age, with the mice having been infected 1, 2, 4, or 6 times, respectively. We evaluated cognitive functions with Y-maze and passive avoidance tasks, and measured neuroinflammation and blood-brain permeability in hippocampus and striatum through immunofluorescence staining. Here we present findings from the 20 month old mice. Mice with a history of CMV exposure displayed spontaneous alternation deficits. Histological evidence revealed evidence of neuroinflammation only in the striatum, with CMV mice displaying elevated GFAP (glial fibrillary acidic protein). There were no differences in IBA1 (ionized calcium-binding adaptor molecule-1) positive cells in either region. Measures of blood-brain barrier permeability are currently undergoing processing. Taken together, our findings suggest that repeated, intermittent viral infection may accelerate cognitive aging and enhance brain inflammation during senescence. While data collection for the 20-month cohort is ongoing, their results will contribute to identifying trends in infection burden and cognitive decline across the lifespan.

Disclosures: N. Barahona: None. **S. Morris:** None. **S.R. Wroblewski:** None. **K. Zwezdaryk:** None. **E.B. Engler-Chiurazzi:** None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.03/C116

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Neuroimaging evidence of neurological complications in adult COVID-19 patients: a systematic review

Authors: *C. A. CENTENO-ROMÁN[1], G. TAPIA NAZARIO[2], I. CASTILLO REYES[2]; [1]Clin. Psychology - Sch. of Behavioral and Brain Sci., Ponce Hlth. Sci. Univ., PONCE, Puerto Rico; [2]Clin. Psychology, Ponce Hlth. Sci. Univ., Ponce, Puerto Rico

Abstract: The emergence of COVID-19 has triggered a global health crisis, leading to millions of confirmed cases and fatalities worldwide. Increasing evidence suggests that COVID-19 may

impact the central nervous system potentially leading to neurological complications. However, due to the novelty of the virus there is limited research on the neurological effects of COVID-19 using neuroimaging techniques. This study aims to explore the prevalence of neurological complications in adult patients with COVID-19 using both structural and functional neuroimaging methods. By describing the associated neuroimaging findings, this research seeks to enhance our understanding of the neurological impact of COVID-19. A systematic review, adhering to PRISMA guidelines, was conducted to explore the literature concerning the impact of COVID-19 on brain structure and function. EBSCOHost and ProQuest databases were searched for studies examining neuroimaging findings related to COVID-19. Articles were screened according to pre-defined inclusion criteria from December 2019 to March 2022. Data extraction gathered key information from the studies. Two authors independently assessed the quality of the research evidence using the JBI Critical Appraisal Tool for Prevalence Studies. Out of 36 articles meeting the inclusion criteria, 18 were excluded following critical appraisal. Data analysis involved qualitative analysis and descriptive measures for all articles included in the study. We identified 18 articles documenting neuroimaging findings in adult patients infected with COVID-19. The included studies featured a total sample age range of 18 to 101 years. Of the total sample of 7,411 patients, 7,074 (95.4%) tested positive for COVID-19, while 337 (4.5%) served as controls. Among the COVID-19 patients, 2,337 individuals (33%) underwent neuroimaging procedures. Within this subgroup, 62.5% were male and 37.5% were female, with 1,104 (47.2%) exhibiting neurological findings. The most common neurological manifestations observed among patients who underwent neuroimaging were cerebrovascular events (26%), followed by white matter abnormalities (12%), and slow brain wave activity (3%). The findings of this study underscore the spectrum of neuroimaging abnormalities observed among adult patients diagnosed with COVID-19. Healthcare providers managing COVID-19 patients exhibiting neurological symptoms should be mindful of these findings and consider obtaining neuroimaging studies for comprehensive assessment. Understanding the diverse neurologic manifestations of COVID-19 is essential for optimizing patient care and advancing our knowledge of the disease.

Disclosures: C.A. Centeno-Román: None. **G. Tapia Nazario:** None. **I. Castillo Reyes:** None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.04/C117

Topic: F.04. Neuroimmunology and Neurovirology

Support: HHMI

Title: Neuroimmune mechanisms of coronavirus disease pathology

Authors: *C. COOK[1], O. GOLDMAN[2], Z. GONG[1], D. BAUTISTA[1,3];
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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), produces several clinical symptoms such as sneezing, coughing, respiratory distress and pain. Most studies have focused on the role the immune system plays in disease pathogenesis. However, the mammalian airways are densely innervated by sensory neurons that can trigger these symptoms, and in some cases, an uncontrolled immune response that causes tissue damage—all hallmarks of COVID-19. Importantly, airway sensory neurons are also directly infected by SARS-CoV-2 in humans and animal models. Very little is known about how these sensory neurons are activated during coronavirus infection and how they contribute to disease pathogenesis. We used a mouse coronavirus model to examine the physiological consequences of viral infection on the nervous system, airway homeostasis and the dysregulation of neuroimmune interactions that promote local and systemic inflammation. We infected wild-type C57BL/6 mice with 25,000 plaque-forming units of the murine coronavirus mouse hepatitis virus strain A59 (MHV-A59). We observed an increase in the number of neutrophils, monocytes, and eosinophils in infected lungs, while characterizing substance P and calcitonin-gene related peptide receptor expression on key inflammatory immune cell populations. Additionally, we observed a significant increase in neuropeptide expression within the lungs on post-infection day three and six ($F(2,12) = [9.222]$, $p = 0.0038$). Whole-body plethysmography recordings of awake, unrestrained MHV-A59 infected mice showed infection-driven increases in key respiratory parameters, including tidal volume ($F(1.097, 6.400) = [8.911]$, $p = 0.0213$), mid-tidal expiratory flow (EF50) ($F(1.875, 10.94) = [3.027]$, $p = 0.0921$), peak expiratory flow ($F(1.727, 10.07) = [4.677]$, $p =0.0405$), and decreased breathing frequency ($F(1.853, 10.81) = [4.091]$, $p = 0.0499$). Collectively, these data support a model whereby during coronavirus infection, lung-innervating sensory neurons may release inflammatory peptides to regulate and promote the influx of inflammatory cells into the airway to drive respiratory dysfunction and disease.

Disclosures: C. Cook: None. **O. Goldman:** None. **Z. Gong:** None. **D. Bautista:** None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.05/C118

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: 1R01MH108466
1R56NS124422
1R01NS124422

Title: Lower gray matter volume and worse white matter hyperintensity burden are associated with faster cognitive decline in adults living with HIV

Authors: *M. BOLDEN, X. JIANG;
Neurosci., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Despite medical advance with modern antiretroviral therapies, HIV-associated neurocognitive disorders remain highly prevalent in people with HIV (PWH). Previous studies have shown that HIV-disease is associated with lower gray matter volume (GMv) and worse white matter hyperintensity (WMH) burden, which in turn correlate with worse neurocognitive performance. Using data from 42 middle-aged to older PWH (age range at baseline 41-69; 12 females at birth; 35 African Americans) who were enrolled in a longitudinal study, we investigated the impacts of lower GMv and worse WMH burden on future cognitive decline. High-resolution T1w structural MRI images ($1x1x1mm^3$) were acquired, and the software package CAT12 (https://neuro-jena.github.io/cat/) was used to detect WMHs and obtain total WMH volume (WMHv) and total gray matter volume (GMv). Total WMHv and GMv were normalized by intracranial volume. Cognitive performance in seven domains was assessed with an established neuropsychological test battery at the baseline visit as well as at the two-year follow-up visit. The seven cognitive domains include verbal fluency, executive function, speed of information processing, working memory, learning, recall, and motor skills, which have been shown to be affected in PWH. T-scores for each cognitive domain were calculated separately using a normative database and were used for statistical analysis. Parametric multiple linear regressions investigated the effects of GMv and WMHv on the difference in domain-specific T-scores between the two study visits, after controlling for T-scores from baseline and demographics (age, race, sex, and education). GMv and WMHv were examined in separate models. Parametric multiple linear regression analyses revealed that lower GMv at the baseline visit correlated with worse decline in working memory (p=.032) and motor function (p=.005) at the follow-up visit, and higher WMHv at the baseline visit correlated with worse decline in working memory (p=.013). By contrast, higher levels of education correlated with less decline in working memory (p=.045) but not motor function (p=.444). These results suggest that lower gray matter volume and worse WMH burden may be associated with faster cognitive decline in adults living with chronic HIV disease. However, higher educational attainment may build brain reserve to ameliorate cognitive decline in PWH.

Disclosures: M. Bolden: None. **X. Jiang:** None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.06/C119

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH RO1DA052209

Title: Cytokine correlations of IL1RN in HIV associated neurocognitive impairment

Authors: *T. J. JANG[1], J. KOURY[2], N. Y. YUAN[2], I. HARAHAP-CARRILLO[2], R. MAUNG[2], M. KAUL[2];
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Abstract: The HIV-1 virus enters the central nervous system (CNS) and causes infection that leads to the development of associated neurocognitive impairment (NCI). Globally, over 38 million people worldwide are diagnosed with HIV, and an estimated 50% of all people living with HIV develop neurocognitive impairments even with regular treatment. The pathology of this neurocognitive impairment lacks sufficient understanding, and no specific treatment exists. IL1B is understood to be a key mechanism in inducing neurotoxicity that leads to neurocognitive impairment in HAND. IL1RN, or IL1RA, encodes the Interleukin 1 receptor antagonist protein and is a competitive inhibitor against IL1A and IL1B by binding to IL1R1. Our understanding of the transient expression level of cytokines during the course of HIV and its associated NCI in brain tissue is incomplete. It has been previously proposed that IL1RN is able to reduce the neurotoxic effects during HIV infection, but the expression of IL1RN decreases with course severity. Understanding the transcriptomic differences in different levels of NCI severity could give new insights into neurotoxicity and dysfunction in the immune system during worsening courses of NCI.
Thus, we analyzed RNA samples derived from the middle frontal gyrus matter (neocortex) of HIV+ patients and age matched non-infected individuals from the National NeuroAIDS Tissue Consortium (NNTC). Demographic data was collected from patients including performance on a range of neurocognitive tests such as executive function, language processing, memory, etc. summarized as a global deficit score (GDS). We show differential gene expression levels of IL1RN compared to a number of cytokines and genes (e.g. LCN2, EPHB2, CCL4, CCL5, IL1A, IL1B) in samples derived from patients with different levels of neurocognitive deficiency using RT-qPCR. We identified high correlations between the expression of IL1RN and CCL3, CCL4, and CCL5 during the most severe cases of HAND, in addition to other differential gene expression correlations between IL1RN and other genes in milder severity cases. We show significant differences in the transcriptomic profile of these sets of cytokines and genes across different NCI severities. Additionally, we used bioinformatic analysis techniques such as principal component analysis (PCA) to illustrate the differences in gene expression across different NCI severity levels.

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Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.07/C120

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant K00NS113455
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Title: Characterization of Monocyte-Derived Microglia from HIV-Seropositive Patients to assess Alpha 7-NAchR Activation Against HIV-induced Neuroinflammation

Authors: *L. ROSARIO-RODRÍGUEZ[1], **A. ORTIZ SANTIAGO**[2], E. RODRIGUEZ[3], V. WOJNA[3];
[1]Intrnl. Med., Univ. of Puerto Rico-MSC, San Juan, PR; [2]Anat. & Neurobio., [3]Intrnl. Med., Univ. of Puerto Rico-Medical Sci. Campus, San Juan, PR

Abstract: Our group and collaborators have demonstrated that the α7-nicotinic acetylcholine receptor (α7nAChR) is increased in monocytes, macrophages, and T lymphocytes of patients with HIV. Recently, others demonstrated that the activation of α7nAChR led to an improvement in locomotor, learning, and memory deficits in a mouse model of HIV-associated neurocognitive disorders (HAND), including a decrease in glial activation in the cerebral cortex and hippocampus. However, the effect of α7nAChR activation in human microglia infected with HIV has not been studied before. We hypothesize that α7nAChR activation in HIV-infected microglia will reduce replication, inflammation, and neurotoxicity caused by HIV. We isolated monocytes from HIV-seropositive patients and HIV-negative donors using ART from our Hispanic-Latino Longitudinal Cohort (IRB#1330422). We treated monocytes with GM-CSF and IL-34 and cultured them until day 14 to develop monocyte-derived microglia (MMG). We quantified the expression of Iba1, microglia markers (TMEM119 and P2RY12), α7nAChR, and HIV-1p24 using super-resolution confocal fluorescence microscopy. Finally, we measured phagocytosis activity. MMG from HIV-seropositive patients presented a variety of ramified and amoeboid morphologies. They showed higher expressions of Iba-1, microglia markers, and α7nAChR than MMG from HIV-negative donors. In addition, MMG from HIV-positive patients tested positive for HIV-1p24. Furthermore, no significant changes in phagocytic activity were seen between MMG from HIV-positive patients and MMG from HIV-negative donors. Our group is the first to report the development of functional MMG from HIV- seropositive patients. Future studies will assess the role of α7nAChR activation in HIV replication, inflammation, and neurotoxicity.

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Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.08/C121

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01DA052826

Title: Exploring the Impact of Frontline Antiretrovirals on Neural Health: Insights from an iPSC Neuroglial Model

Authors: *B. C. CUI[1], E. NICKOLOFF-BYBEL[1], A. ANGELUCCI[2], X. SHI[1], Y. SU[2], C. AKAY-ESPINOZA[1], K. M. CHRISTIAN[2], K. L. JORDAN-SCIUTTO[1];
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Abstract: Despite significant strides made in antiretroviral therapy, people with HIV (PWH) continue to endure disproportionate challenges associated with neuronal disorders and neurocognitive decline. While antiretrovirals (ARVs) have substantially prolonged their life expectancy, emerging evidence suggests they may also trigger distinct neuronal injury alongside persistent neuronal inflammation stemming from glial cell activation due to chronically suppressed infection. However, studying such neuronal damage in PWH presents inherent challenges, given the difficulty of obtaining human tissue samples and the incompatibility of rodent cell models with HIV. In this study, we demonstrate the utility of an induced pluripotent stem cell model comprising excitatory cortical neurons and astrocytes to investigate the impact of frontline ARVs on neuronal health and function. Cocultures of induced neurons (iN) and astrocytes (iA) were exposed to increasing concentrations of ARVs, guided by their reported peak plasma concentration (Cmax) within human CNS, for 10-14 days. Neuronal function assessments were taken using a multi-electrode array, inflammation profiles were characterized by cytokine quantification, and transcriptomic changes were tracked by sequencing. Using these approaches, we observed that higher ARV concentrations, albeit not inducing overt cell death, significantly diminished neuronal firing. Moreover, treatment with ARVs at 3X Cmax led to a significant reduction in glutamate uptake by iA, indicating alterations in astrocytic function at therapeutic concentrations. Single-cell RNA sequencing analysis revealed distinct transcriptional profiles corresponding to various ARV treatments across different cell types. These findings are poised to advance our understanding of the interplay between frontline ARVs and CNS health, ultimately aiding the development of adjunct strategies to mitigate adverse effects of ARVs and bolster the well-being of PWH.

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Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.09/C122

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NIDA Grant 1U01DA053630-01
NIH T32 NS061847

Title: The transcriptomic and epigenomic impact of HIV and opioid use across human prefrontal cortex cell types

Authors: *A. GREEN[1], X. CHEN[2], J. BUCHANAN[2], Y. LEE[3], J. LI[4], D. R. BURROWS[5], A. WANG[6], K. GAULTON[2], *T. RANA[2], E. A. MUKAMEL[7];
[1]Neurosciences, [3]Pediatrics, [4]Dept. of Cognitive Sci., [5]MRC Ctr. for Neurodevelopmental Disorders, [6]Ctr. for Epigenomics, [2]UC San Diego, San Diego, CA; [7]Cognitive Sci., UC San Diego, La Jolla, CA

Abstract: Despite modern treatment, HIV-associated neurocognitive disorders persist in nearly half of the 39 million people living with HIV. HIV and opioid use disorder (OUD) are intertwined epidemics, with 20-50% of people with HIV being prescribed opioids for chronic pain. In turn, one third of individuals with OUD administer drugs through injection, elevating risk of HIV infection. Opioids exacerbate cognitive dysfunction and inflammation in people living with HIV, yet little is known of how concurrent HIV and OUD impact gene expression and regulation across human brain cell types. Understanding the cell-type specific mechanisms that underlie HIV and OUD's neuropathogenesis will critically inform the development of targeted therapies.
Using post-mortem prefrontal cortex tissue, we characterized changes in gene expression and regulation within the context of HIV and/or OUD across neuronal and glial cell types. We analyzed multiomic sequencing data (single nuclei RNA-sequencing and single nuclei ATAC-sequencing) and applied advanced computational methods to investigate the role of gene expression and regulation in HIV, OUD, and HIV/OUD compared to controls. We profiled 73,222 cells from 21 donors, including 7 HIV cases, 5 OUD, 4 HIV/OUD, and 5 controls. This donor group consists of 5 females and 16 males in the age range of 27-82 years. We clustered and annotated cells in 23 neuronal and glial cell types, finding 323 genes with significant differences in expression between groups (false discovery rate <0.01; HIV vs OUD, HIV vs HIV/OUD, OUD vs HIV/OUD). Using the multiome profiles, we are investigating the impact of HIV and OUD on neuronal and glial epigenomes. In addition, we are characterizing epigenetic signatures of resilience to neuroinflammation in HIV, OUD, and HIV/OUD groups. Results from this study yield insight into the impact of HIV and/or OUD across brain cell types, identifying potential targets for therapeutic intervention.

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Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

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Program #/Poster #: PSTR335.10/C123

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Institutes of Health grant U01DA053600
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National Institutes of Health Office of Research Infrastructure grant S10OD026880
National Institutes of Health Office of Research Infrastructure grant S10OD030463
National Center for Advancing Translational Sciences Clinical and Translational Science Awards grant UL1TR004419

Title: Independent and synergistic transcriptional impacts of opioid/cocaine substance use disorder and HIV on human ventral midbrain cell types: a cohort study at the Manhattan HIV Brain Bank

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Abstract: For people with HIV (PWH), substance use disorders (SUDs) are a prominent neurological risk factor. Individuals who inject drugs of abuse are at heightened risk of infection and comprise ~10% of PWH globally, and both HIV and SUD impact cell-level dopaminergic brain function, allowing for potentially deleterious combined effects. HIV persists in “reservoirs” including in the brain during antiretroviral therapy and is associated with long-term development of neurocognitive disorders (for ~50% of PWH). HIV viral load appears to be heaviest in dopaminergic regions and corresponds with decreasing dopamine levels, suggesting increased vulnerability to damage in these regions. Similarly, SUD is associated with decreased dopaminergic pathway responsiveness for most drugs of abuse. Insight about cellular changes related to HIV, SUD, or both is limited, but would be valuable for informing interventions. Here, we explore cell-type-specific transcriptional alterations in chronic HIV and opioid/cocaine SUD in postmortem substantia nigra, a major dopaminergic center, performing single-nucleus RNA sequencing for 90 donors (45 HIV+/SUD+; 17 H+/S-; 15 H-/S+; 13 H-/S-; ~200,000 nuclei total). Using abnormality-tolerant analysis of 20,000 highly varying genes, we have identified expression changes in dopaminergic/GABAergic neurons (central components of intercellular signaling) and microglia (important HIV reservoir cells and inflammatory response mediators).

We have also identified functional gene groups with highly coordinated altered expression across donors. We find that HIV but not SUD is associated with reduced dopamine transporter transcription in dopaminergic neurons; whereas SUD involves increased excitability, impaired postsynaptic function, and reduced-frequency presynaptic release. We also observe HIV/SUD synergies, which for controlled HIV may permit HIV viral replication and mediate cytotoxic damage to/loss of dopaminergic neurons. In viremic synergy, HIV ungates coordinated opioid/cocaine SUD impacts on GABAergic and dopaminergic neurons, indicating SUD-mediated dopaminergic disinhibition.

Disclosures: A. Wilson: None. **M.M. Jacobs:** None. **T.Y. Lambert:** None. **A. Valada:** None. **G. Meloni:** None. **E. Gilmore:** None. **J. Murray:** None. **S. Akbarian:** None. **S. Morgello:** None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.11/C124

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01 MH087332
NIH Grant R01 DA052209
NIH Grant P50 DA026306
NIH Grant F31 NS129462

Title: Modulation of neuroinflammation by methamphetamine - implications for HIV-associated brain injury.

Authors: *S. TAYABALLY[1], M. KAUL[2], J. KOURY[3], R. MAUNG[4];
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Abstract: Modulation of neuroinflammation by methamphetamine - implications for HIV-associated brain injury.
Sakina Tayabally[1], Jeffrey Koury[1,3], Ricky Maung[1] Marcus Kaul[1,2]
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Methamphetamine (METH) is known for its strong addictive properties and high abuse rates, especially among people living with HIV (PLWH) receiving combination anti-retroviral therapy (cART). The interaction between HIV and METH leads to higher viral titers and appears to

exacerbate the progression of HIV-associated neurocognitive impairment (NCI) and underlying neuronal damage. Both, HIV and METH have been shown to induce inflammatory processes which presumably contribute brain injury and NCI. Peripheral HIV-infected monocytes/macrophages infiltrate and carry the virus into the brain and are known to release neurotoxins and pro-inflammatory factors. The virus also infects microglia. Therefore, our research examined the in vitro effects of METH on different cell types, including monocytic THP1 cells, the human microglial cell line HMC3, and induced pluripotent stem cell-derived microglia. We found that METH reduced the levels of pro-inflammatory cytokines like TNF-α and IL6, along with anti-inflammatory and antiviral cytokine IFNβ. It also downregulated IFN-γ, which is essential for activating monocytes and macrophages, suggesting a reduction in immune response. Additionally, we observed decreased protein expression of CXCL10/IP-10, a chemokine regulated by IFN-γ. Our results indicate that METH reduces the anti-viral immune response and the associated processes of inflammation, which suggests that METH engages other pro-inflammatory pathways that lack anti-viral and neuroprotective effects.
Supported by NIH, R01 MH087332, R01 DA052209 and P50 DA026306 to M.K., F31 NS129462 to JK

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Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.12/C125

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R01 MH105330
NIH R01 DA052209

Title: Neuronal Injury Associated with HIV Infection Requires Macrophage-derived Cysteinyl-Leukotrienes: Regulation by Methamphetamine

Authors: *M. KAUL[1], K. E. MEDDERS[3], A. B. SANCHEZ[5], R. SHAH[1], D. OJEDA-JUÁREZ[4], R. MAUNG[6], B. GELMAN[7], A. J. ROBERTS[8], N. Y. YUAN[2];
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Abstract: Viral infections, such as with human immunodeficiency virus (HIV)-1, can cause neurocognitive impairment and severe brain injury. Microglia and macrophages (MΦ) infected with HIV-1 or activated by its envelope protein gp120 exert neurotoxicity. We found previously that signaling via p38 mitogen-activated protein kinase (p38°MAPK) is essential to the

neurotoxicity of HIVgp120-stimulated MΦ. However, the associated downstream pathways remained elusive. Here we show that cysteinyl-leukotrienes (CysLT) released by HIV-infected or HIVgp120 stimulated MΦ downstream of p38°MAPK critically contribute to neurotoxicity. SiRNA-mediated or pharmacological inhibition of p38°MAPK deprives MΦ of CysLT synthase (LTC4S) and, pharmacological inhibition of the cysteinyl-leukotriene receptor 1 (CysLTR1) protects cerebrocortical neurons against toxicity of both gp120-stimulated and HIV-infected MΦ. Components of the CysLT pathway are differentially regulated in brains of HIV-infected individuals and a transgenic mouse model of NeuroHIV (HIVgp120tg). Moreover, genetic ablation of LTC4S or CysLTR1 prevents neuronal damage and impairment of spatial memory in HIVgp120tg mice. Methamphetamine (METH) use is frequent among people living with HIV-1 and aggravates HIV-associated neurocognitive impairment. Exposing MΦ to the HIV LTR mimic ssRNA40 in the presence of METH can induce a significant upregulation of LTC4S and CysLTR1. Altogether, our findings suggest a novel critical role for cysteinyl-leukotrienes in HIV-induced brain injury that is further regulated by comorbid METH use. Supported by NIH, MH105330 and DA052209 to M.K.

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Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.13/C126

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant DA055568

Title: Dimethyl fumarate ameliorates deficits of cognition, mood, and opioid abuse in mice exposed to hiv-1-tat protein and/or morphine

Authors: *J. P. MCLAUGHLIN[1], H. HAMMOND[2], S. EANS[2], T. J. CIRINO[1], S. THANGAVEL[3], M. J. KAUFMAN[4];
[1]Pharmacodynamics, [2]Univ. of Florida, Gainesville, FL; [3]Texas A& M University, Col. of Pharm., College Station, TX, ; [4]McLean Hosp, Belmont, MA

Abstract: Although modern antiretroviral therapy effectively suppresses HIV replication, people living with HIV-1 still develop HIV-Associated Neurocognitive Disorder (HAND). Moreover, opioid use disorder (OUD) comorbid with HIV-1 infection exacerbates both the severity and progression of HAND. We hypothesize that conditional expression of the HIV-1 protein transactivator of transcription (Tat) and exposure to opioids in animal models synergistically induces changes analogous to HAND, including deficits in neurophysiology (increased reactive oxygen species (ROS), and reduced Brain-Derived Neurotropic Factor (BDNF) and

mitochondrial biogenesis) and behavior (increased drug-seeking and depression-like behaviors, while impairing learning and memory performance). Testing this, we used the iTat-tg mouse model and Tat-null control mice to demonstrate that a 7-day expression of Tat protein increases morphine-seeking behavior, with a 2.5-fold potentiation of morphine conditioned place preference and increased morphine consumption in a two-bottle choice (TBC) assay. Moreover, exposure to morphine and Tat, alone and together, produce depression-like increased immobility in a tail suspension test and reduced voluntary consumption of saccharine in a TBC assay, and further reduced novel object recognition to demonstrate impaired learning and memory performance. Notably, oral administration of Dimethyl Fumarate (DMF) dose-dependently ameliorated these effects to varying degrees in mice exposed to Tat protein and/or morphine. As DMF is known to reduce ROS levels and increase BDNF levels and activate the master antioxidant transcription factor Nuclear Factor erythroid 2-related factor 2 (NFE2L2), leading to reductions in oxidative stress and improved mitochondrial function and biogenesis, brains were isolated from studied mice to assess these variables, with results to be discussed. Collectively, our findings may suggest new mechanistic insights into the dysfunction induced by exposure to HIV-Tat protein and opioids, while demonstrating that the DMF, currently clinically approved for treating multiple sclerosis, could benefit patients with HIV-1, OUD, or the comorbid disorder.

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Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.14/C127

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant DA044552
NIH Grant DA044552-03S1
NIH Grant DA057197
NIH Grant NS060632
NIH Grant MH122241

Title: The effects of chronic cocaine exposure and neuroHIV with cART on the function of astrocytic voltage-sensitive K^+ channels in the reward circuits

Authors: *L. CHEN, S. L. CASSODAY, D. IMERI, L. AL-HARTHI, X.-T. HU;
Dept. of Microbial Pathogens and Immunity, Rush Univ. Med. Ctr., Chicago, IL

Abstract: Cocaine (COC) is a highly addictive and widely abused psychostimulant. Chronic exposure to COC induces neuronal hyperactivity in the medial prefrontal cortex (mPFC, one of the critical regulators of cognition and addiction), which may contribute to the mechanism

underlying COC addiction. This effect of COC is worsened by neuroHIV. Although combined antiretroviral therapy (cART) suppresses HIV replication, improves immune function, and prolongs life of HIV^+ individuals, the prevalence of HIV-associated neurocognitive disorders (HAND) occurs in ~50% of people living with HIV. Previous studies indicate that many antiretroviral medicines (ARVs) can induce neurotoxicity in the peripheral and central nervous system. Lamivudine (a.k.a. 3TC) is a nucleoside reverse transcriptase inhibitor (NRTI), and one of the three ARVs (co-formulated with abacavir, ABC; and dolutegravir, DTG) that form Triumeq (a 1st-line cART regimen approved and recommended by FDA to treat HIV/AIDS). Our previous studies demonstrated that chronic Triumeq treatment induces hyperactivity of mPFC neurons by abnormally enhancing voltage-gated Ca^{2+} channel function, and reducing K^+ channel activity in adolescent rats. However, little is known whether such neuronal dysfunction results from the alteration in the synaptic/intrinsic excitability of neurons *per se*, dysfunction of astrocytes that disturbs extracellular homeostasis of glutamate and K^+ levels, or both. Additionally, the effects of chronic COC exposure and neuroHIV combined with cART on extracellular K^+ homeostasis mediated by astrocytes, and its underlying mechanism is also unknown. To fill this knowledge gap, we are assessing the functional activity of voltage-sensitive K^+ channels in astrocytes using brain slices containing the mPFC from HIV-1 transgenic (HIV-1 Tg) rats (5-6-month of age), a rodent model of neuroHIV after cART, in the absence of active HIV-1 replication but the expression of multiple viral proteins. Age matched F344 non-Tg rats are used as control. Electrophysiological approaches (whole-cell patch-clamping) are used to assess the dysfunction of live mPFC astrocytes in rat brain. To assess the chronic effects of cART, rats are treated with repetitive daily s.c. injection of Triumeq for 28 days. For evaluating chronic COC effects, rats are trained to self-administer (SA) COC for 14 days followed by 2-5 days of withdrawal. COC-SA starts on day 15 of Triumeq injection. This study will determine whether, how, and to what extent, chronic cART alters the effects of neuroHIV, with or without Coc-SA, on the functional activity of voltage-sensitive K^+ channels in mPFC astrocytes in the brain.

Disclosures: L. Chen: None. **S.L. Cassoday:** None. **D. Imeri:** None. **L. Al-Harthi:** None. **X. Hu:** None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.15/C128

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant R01DA035714
NIH grant R01DA041932
NIH grant DA057866

Title: Sri-47056 a structure-based allosteric modulator attenuates hiv-1 transactivator of transcription (tat) protein effects on dopamine release in the caudate putamen of inducible transgenic mice

Authors: *A. C. JIMÉNEZ-TORRES[1], O. MOUKHA-CHAFIQ[2], S. ANANTHAN[3], C. E. AUGELLI-SZAFRAN[2], J. ZHU[1];
[1]Drug Discovery and Biomed. Sci., Col. of Pharmacy, Univ. of South Carolina, Columbia, SC; [2]Dept. of Chemistry, Scientific Platforms Div., Southern Res., Birmingham, AL; [3]Div. of Neurosci., Natl. Inst. on Drug Abuse, Natl. Inst. of Hlth., North Bethesda, MD

Abstract: The HIV-1 Tat protein has been considered a major pathogenic factor in the development of HIV-associated neurocognitive disorders (HANDs) through the disruption of normal monoamine neurotransmission. We have demonstrated that Tat binds to allosteric binding sites(s) on human dopamine transporter (hDAT) and acts as a negative allosteric modulator. Induction of Tat expression in inducible Tat transgenic (iTat-tg) mice by a systemic administration of doxycycline (Dox) increases extracellular dopamine (DA) levels in the caudate putamen (CPu). Our recent findings demonstrated that the novel allosteric modulator, SRI-32743, alleviates the increased DA release in the baseline of phasic dopamine release, the potentiation of cocaine reward, and the deficit in cognition in iTat-tg mice. This study determined whether SRI-47056, an analog of SRI-32743, allosterically modulates DAT to attenuate Tat-induced effects on extracellular dopamine dynamics. SRI-47056 displayed an improved ADME profile and potency to inhibit [^{3}H]dopamine uptake in CHO-K1 cells expressing hDAT (IC_{50} value, 0.96 ± 0.05 μM, E_{max} value 53.05 ± 12.69) compared to SRI-32743 (IC_{50} value, 9.68 ± 0.99 μM, E_{max} value 67.87 ± 9.72). The enantiomers of SRI-47056, (R)-(+)-SRI-47056 and (S)-(−)-SRI-47056 partially inhibiting *in vitro* [^{3}H]DA uptake (IC_{50} value 2.79 ± 0.62 and 0.37 ± 0.05, respectively) and [^{3}H]WIN35,428 binding in WT hDAT (IC_{50} value 1.74 ± 0.87 and 0.93 ± 0.16, respectively). Notably, bath applied range of concentrations of SRI-47056 (0.1 nM- 1μM) did not alter the baseline phasic-like DA release in CPu from C57BL/6 mice but 1 μM of SRI-47056 increased the baseline tonic-like DA release. Moreover, a single dose of SRI-47056 (i.p. 1 or 10 mg/kg) maintains basal locomotor activity in C57BL/6 mice compared with vehicle group. However, a systemic single dose of SRI-47056 (i.p. 0.1 or 1 mg/kg) 30 min prior to sacrifice reversed the increase of phasic dopamine release in CPu in Dox-treated iTat-tg mice compared with the saline-treated group. These findings provide further support to the emerging concept of allosteric modulation of DAT function as a potential therapeutic approach modulating Tat-DAT interactions to normalize DA neurotransmission in HAND.

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Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.16/C129

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DA054992
DA058586
GM154632

Title: Drug Repurposing for the Prevention of Dementia Among People Living with HIV: Focus on the Renin-Angiotensin System

Authors: *M. SHTUTMAN[1], J. MAGAGNOLI[2], M. AKSENOVA[3], A. SIKIRZHYTSKAYA[4], T. CUMMINGS[2], I. TYAGIN[5], G. SCHOOLS[4], I. K. SARIYER[6], R. M. BOOZE[7], M. WYATT[4], I. SAFRO[8], S. SUTTON[2];
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Abstract: We utilized an artificial intelligence (AI)-based biomedical literature mining system to uncover genes associated with human immunodeficiency virus (HIV)-related cognitive dementia. We found genes related to the renin-angiotensin system, which is also a target of FDA-approved medications for hypertension. We therefore determined the effects of angiotensin-converting enzyme inhibitors (ACEi) on dementia among people living with HIV (PLWH) by mining a large, longitudinal medical record database. This retrospective cohort study was conducted using data from the US Department of Veterans Affairs Informatics and Computing Infrastructure (VINCI). The study utilized a cohort of PLWH stratified according to pharmacy dispensation of ACEi that can cross the blood brain barrier (BBB) versus those unexposed to ACEi. The study outcome was the development of dementia. At one and five years, the ACEi BBB cohort had a lower rate of dementia compared to the unexposed cohort. A sub-analysis evaluated the incidence of dementia among PLWH exposed to ACEi BBB compared to PLWH exposed to ACEi that do not penetrate the BBB (ACEi noBBB). The result was consistent with the primary outcome, namely the ACEi BBB cohort had a lower rate of dementia. Additionally, we conducted a study among PLWH and having a past medical history of substance abuse disorder. The results were consistent with the primary study, in that patients in the ACEi BBB cohort had a lower rate of dementia at five years. Further, in a model study, treatments with BBB-penetrating ACEi and angiotensin receptor blockers (ARBs) protects cerebral organoids from HIV neurotoxicity. Transcriptomic analysis revealed that ACEis and ARBs regulate pathways involved in neuroprotection and viral suppression. Collectively, this research suggests a possible link between blood-brain barrier crossing renin-angiotensin drugs and treatment of dementia among PLWH.

Disclosures: M. Shtutman: None. **J. Magagnoli:** None. **M. Aksenova:** None. **A. Sikirzhytskaya:** None. **T. Cummings:** None. **I. Tyagin:** None. **G. Schools:** None. **I.K. Sariyer:** None. **R.M. Booze:** None. **M. Wyatt:** None. **I. Safro:** None. **S. Sutton:** None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.17/C130

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 1K01NS129895-01
Emory Center for AIDS Research Grant P30AI050409
Borroughs Wellcome Fund

Title: GPER activation, via G-1 agonist, may reduce HIV-induced neuroinflammation.

Authors: *J. J. DE VASTEY, K. DAVIS, K. WILLIAMS;
Envrn. & Hlth. Sci., Spelman Col., Atlanta, GA

Abstract: Although combined antiretroviral therapies have been effective in inhibiting viral replication, HIV-associated neurocognitive disorders (HAND) affect 30-50% of people living with HIV (PLWH). Antiretroviral therapies have allowed PLWH to live longer lives, with the median age of this population reaching 50 years old. While this population ages, HAND prevalence is predicted to rise. Thus, understanding how aging with HIV affects the brain is integral to finding novel HAND therapeutics. Neuronal damage caused by HIV-induced macrophage and microglia inflammatory activation is a key part of HAND pathogenesis. Employing endogenous cell signaling pathways might reduce this neuroinflammation. Previous studies have highlighted 17β-estradiol's neuroprotective effects and indicate that it may be able to suppress HIV-induced neurotoxicity via classical estrogen receptor activation. While the classical receptors Erα and Erβ are well-studied, less is known about the non-classical estrogen receptor GPER1. Some studies have revealed the non-genomic protective role of GPER1; however, the effect of GPER1 on HIV-induced neuroinflammation remains unclear. We hypothesized that activation of GPER1 via GPER1 inducer G-1 will reduce HIV-induced neuroinflammation. To test this, we used a dual cell *in vitro* model of human monocyte-derived macrophages (MDMs) and rat cortical neurons. GPER1 was blocked with a specific antagonist (G15) in MDMs before stimulation with inactivated HIVada in the presence or absence of G-1. Whole-cell lysates and conditioned medium were collected at various time points. We found that macrophage-conditioned media from cells treated with G-1 suppressed the neurotoxic effect of HIV. Additionally, G-1 reduced inflammatory phenotypes in HIV-infected macrophages in a GPER1-dependent manner. G1 and HIV cotreatment reduced HIV-induced apoptotic protein, BAX, but increased antioxidant proteins like SIRT3 and SOD1 compared to HIV alone. In conclusion, estrogen signaling via GPER1 may reduce neuroinflammation and be a gateway to developing a novel therapeutic for HAND.

Disclosures: J.J. de Vastey: None. **K. Davis:** None. **K. Williams:** None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.18/C131

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Burroughs Wellcome Fund
1K01NS129895-01
P30AI050409

Title: Dose-dependent estrogen regulation of HIV-induced Neuroinflammation via the non-classical GPER receptor.

Authors: J. DE VASTEY[1], ***K. S. WILLIAMS**[2];
[1]Spelman Col., Stone Mountain, GA; [2]Spelman Col., Lithonia, GA

Abstract: Despite the success of combined antiretroviral treatments, 30-50% of persons living with HIV are affected by HIV-associated Neurocognitive Disorders (HAND). As persons living with HIV age, it is predicted that the prevalence of HAND will increase. Therefore, understanding how aging with HIV affects the brain is important for therapeutic discovery. Macrophages and microglia (M/M) play pivotal roles in the pathogenesis of HIV-associated neurocognitive disorders. The ensuing inflammatory M/M activation causes neuronal damage. Studies utilizing exogenous anti-inflammatory and antioxidants to mitigate disease progression have been unsuccessful; however, targeting endogenous pathways, such as estrogen signaling may be advantageous. Loss of estrogen due to the onset of menopause leads to reduced cognitive functions in women while classical estrogen receptors have been shown to be neuroprotective. It has been reported that 17β-estradiol can inhibit HIV infection in primary macrophages and peripheral blood mononuclear cells and protect neurons against HIV proteins. Recent studies have elucidated the protective roles of non-classical estrogen receptor GPER1, however, how it contributes to HIV-induced neuroinflammation is unknown. We hypothesize that activation of GPER1 via natural estrogen, 17β-estradiol will reduce HIV-induced neuroinflammation. To test this, we utilized a dual cell *in vitro* model consisting of human monocyte-derived macrophages (MDMs) and rat cortical neurons. All estrogen receptors were blocked individually with specific antagonists in MDMs prior to HIV stimulation with inactivated HIVada in the presence and absence of various doses of 17β-estradiol. Cytoplasmic lysates, RNA and conditioned medium were collected at various time points. We found that 17β-estradiol suppressed HIV-induced neurotoxins production and upregulated secretion of growth factors, in a dose-dependent manner. Blocking GPER receptor with G15 reversed 17β-estradiol's ability to reduce HIV-induced neurotoxicity. High doses of 17β-estradiol (30nM) also increased various antioxidant proteins while decreasing inflammatory pathways. Given these studies, increased estrogen signaling, via GPER1, may reduce neuroinflammation seen during neurodegenerative disorders, such as HIV-associated neurocognitive disorders.

Disclosures: J. de Vastey: None. **K.S. Williams:** None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR335.19/C132

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DA056288
DA013137
DA059310
NS100624
GM109091

Title: Suppression of HIV-induced neurotoxicity and synaptodendritic injury by the selective estrogen receptor β; agonist S-Equol

Authors: *R. K. OTT[1], K. A. MCLAURIN[2], H. LI[1], R. M. BOOZE[1], C. F. MACTUTUS[1]; [1]Psychology, Univ. of South Carolina, Columbia, SC; [2]Dept. of Pharmaceut. Sci., Univ. of Kentucky, Lexington, KY

Abstract: HIV-1 Associated Neurocognitive Disorders (HAND) remain one of the most consequential sequelae of HIV-1 infection. Pathologically, neurocognitive injury (NCI) resulting from HAND results in a loss of spines and circuit connectivity, manifesting as progressive neurodegeneration with marked deficits in attention, memory, and executive function. At the molecular level, neurotoxic HIV-1 viral proteins induce prominent alterations to dendritic spine dynamics and function; however, the signaling pathways from which these aberrations spur are not fully understood. Rho GTPases are known to orchestrate synaptodendritic dynamics both autonomously and non-autonomously through activation of secondary effector signaling cascades, providing ubiquitous spatiotemporal control over the actin cytoskeleton. Previously, overactivation of the NogoA-NgR3/PirB-RhoA pathway has been shown to preclude synaptic dysfunction and loss by promoting actin disassembly in a rodent model of EcoHIV infection. S-Equol, a selective estrogen receptor β; agonist (SERBA), promotes synapse stabilization and maintenance by modulating filamentous actin dynamics; however, its therapeutic utility in mitigating the specific effects of NogoA-NgR3/PirB-RhoA pathway overactivation has yet to be evaluated. Thus, HIV-1 transgenic (HIV-Tg) and control animals were treated with either a daily oral dose of S-Equol (0.2 mg) or vehicle and we examined PirB expression. Immunohistochemical analysis of PirB expression in the prefrontal cortex suggested an increase in HIV-1 Tg animals relative to controls ($p \leq 0.052$), and consequent to 60 days of S-Equol treatment, this increase was mitigated. Further, HIV-Tg animals treated with vehicle exhibited alterations in spine morphology consistent with previously described effects of the HIV-Tg transgene. Taken together, these data suggest the beneficial effects of S-Equol in cognitive performance previously reported may be attributed to its ability to enhance neuroregeneration.

Disclosures: R.K. Ott: None. **K.A. McLaurin:** None. **H. Li:** None. **R.M. Booze:** None. **C.F. Mactutus:** None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

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Program #/Poster #: PSTR335.20/C133

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DA056288
DA13137
DA059310
NS100624
GM109091

Title: The crosstalk of β-Amyloid aggregation and synaptic dysfunction: aging HIV-1 transgenic rat brain

Authors: *H. LI[1], K. A. MCLAURIN[2], C. F. MACTUTUS[1], R. M. BOOZE[3];
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Abstract: The prevalence of HIV-1-associated neurocognitive disorders (HAND) represents a challenging clinical crisis in older HIV seropositive individuals, relative to younger. In aging, the morphological changes of synaptodendritic spines of pyramidal neurons in the prefrontal cortex represent neuronal degeneration, specifically, the size and shape of dendritic spines which relates to their structural plasticity, learning, and memory processes. However, the neural pathogenesis of aged HIV-1 seropositive individuals remains unknown. To explore this knowledge gap, β-amyloid aggregates were studied in the brains of aging (>16 months of age) HIV-1 transgenic (Tg) rats. Synaptodendritic spine changes were also analyzed to identify synaptic dysfunction in aging animals. The aggregation of β-Amyloid was elevated in the prefrontal cortex region of HIV-1 Tg rats (250%), relative to controls [$F(1,44) = 21.3$, $p \leq 0.0001$]. Moreover, there was a significant interaction with biological sex [$F(1,44) = 7.5$, $p \leq 0.009$] with increased β-Amyloid accumulation most pronounced in males ($p<0.001$), and not seen in females ($0.05<p<0.10$). The factor of biological sex also influenced the manner in which dendritic spine dysmorphology was expressed in the HIV-1 Tg animals. The HIV-1 Tg male animals exhibit a population shift towards increased dendritic spine head diameter and decreased dendritic spine backbone length, consistent with a "stubby" dendritic spine phenotype. In contrast, the HIV-1 Tg female rodents exhibit a population shift towards decreased dendritic spine head diameter and increased dendritic spine backbone length, supporting a "thin" or "filopodia"-like phenotype. Overall, it appears that the HIV-1 Tg animals have an increased relative frequency of dendritic branches at lower branch orders relative to control rats. The association of β-amyloid aggregates and synaptodendritic spine changes suggests abnormal protein accumulation in certain brain regions impacts synaptodendritic complexity and leads to neuronal synaptic dysfunction in HIV-1-associated neurocognitive disorders.

Disclosures: H. Li: None. **K.A. McLaurin:** None. **C.F. Mactutus:** None. **R.M. Booze:** None.

Poster

PSTR335: Neuroinflammation: HIV and Infections

Location: MCP Hall A

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Program #/Poster #: PSTR335.21/C134

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Title: A proposed mechanism for the generation of neuroinflammation in the Substantia Nigra of the HIV-1 Transgenic rat.

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Abstract: The development of the HIV-TG rat from our laboratory, as a model for HIV infection, has produced well over 100 publications from many laboratories. But, over the time frame of these publications, the nature of HIV infection has evolved. The quality of life and longevity of patients has improved. This has been due to the development of very effective antivirals. However, noninfectious HIV comorbidities have emerged as a continuing medical challenge. Among the different organ-based comorbidities, the nervous system is notably affected, resulting in motor problems or cognitive problems (i.e. HAND). Therefore, updated experimental model systems are needed. The initiating event, which causes the comorbidities is a chronic inflammatory response due to the low levels of uneradicated HIV or HIV proteins. This low level of virus is considered the start of the chronic neuroinflammatory process, but subsequent steps leading to cell dysfunction and death need to be elucidated. In the HIV- TG rat we previously demonstrated that HIV transgene products are produced and, in particular, GP-120 has been identified in the sera and CSF. Moreover, since the rat possesses a CXCR4 receptor capable of binding to the transgenic GP120, we proposed a mechanism for selective cell death based on that interaction. These characteristics make the HIV-1 TG rat a suitable model for studying HIV CNS comorbidities. It has been established that HIV- infected patients can present with Parkinsonian like symptoms. Initially we identified motor abnormalities in the HIV-1 TG rat consistent with Parkinsonism and then characterized the pathology found in the dopamine system. In the present study we confirm that the HIV/ GP-120 receptor CXCR4 is on glial cells in the Substantia Nigra (SN) and caudate/putamen by immunohistochemistry in the HIV-1 TG rat. In addition, using immunohistochemistry for the enzyme Monoamine Oxidase B, the glial

cells in the SN were found to be positive for this enzyme. Monoamine Oxidase B is responsible for degrading dopamine. This data suggests that as these glial cells are targeted by GP-120, abnormalities to their dopamine degradation capacity may occur. Improper degradation of dopamine results in a localized production of free radicals. The cellular damage from this process can then contribute to the development of neuroinflammation as the astrocytes and microglia respond to the developing cellular damage. This can then in turn, lead to accumulating damage to SN neurons including their projections to the caudate nucleus. Histological identification and localization of these substances in the SN provide a framework for studying a possible mechanism of chronic neuroinflammation.

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Title: Identification of EcoHIV-infected cells in microglia-manipulated transgenic mice

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Abstract: Combination antiretroviral therapy (cART) has dramatically improved the quality of life for people living with HIV (PLWH); however, over 4 million PLWH who are over 50 years of age have the accompanying HIV-associated Neurocognitive Disorders (HAND). To understand how HIV impacts the central neuronal system, a replicable and robust model of HIV is necessary. Previously, we generated a novel biological system using chimeric HIV (EcoHIV) inoculation in a rat model system and investigated neurocognitive impairments and synaptic dysfunction which may underlie HAND. Nevertheless, there remains a significant challenge to clarify EcoHIV neuroanatomical distribution, especially the differential expression of EcoHIV in multiple cell types in the brain. In the current study, therefore, we modified EcoHIV with mScarlet fluorescence labeling which was then injected into *Tmem119-EGFP* knock-in mice (enhanced green fluorescence protein primarily in microglia) to elucidate if microglia are the

major cell type for viral expression and a prominent reservoir of HIV in brain. Our data show that: 1) *in vitro*, EcoHIV-mScarlet fluorescence signals were predominantly localized in microglia morphology type of cells among primary rodent brain cells; 2) *in vivo*, injection of EcoHIV-mScarlet into *Tmem119-EGFP* mice induced significant expression of HIV in mouse brain. The co-localization of mScarlet and EGFP signals suggest that microglia represent the main cell type harboring HIV in the brain. Overall, EcoHIV in rodents offers a valuable biological system to study microglia alterations and viral reservoirs in the brain, as well as the neurological mechanism of HIV-associated neurocognitive disorders.

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Poster

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NS060632
MH122241

Title: Sars-cov-2 igg antibodies induces hyperactivity of medial prefrontal cortex pyramidal neurons in both non-tg and hiv-1 tg rats that self-administer cocaine

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Abstract: Neurocognition is a crucial function for everyday life and controlled by certain brain regions, including the medial prefrontal cortex (mPFC), that work interactively to regulate attention, memory, and learning. Neurocognitive deficits are a common feature with some brain diseases, including but not limited to, COVID-19 (with SARS-CoV-2 infection), HIV-Associated Neurocognitive Disorder (HAND, with HIV infection), and drug addition, such as cocaine use disorder (CUD). We have previously demonstrated that the SARS-CoV-2 spike protein induces hyperactivity of mPFC pyramidal neurons in both non-transgenic (Tg) and HIV-1 Tg rats that self-administer cocaine. But how the immune responses to SARS-CoV-2 infection affect mPFC neuron function in HAND and/or CUD has yet to be investigated. To address this knowledge gap, we used combined rat models of neuroHIV (HIV-1 Tg rats) and cocaine self-administration (Coc-SA) to determine the effects of immune responses-induced dysfunction of

mPFC neurons. Rats underwent 2 weeks of Coc-SA followed by a 3-week withdrawal, with additional drug-seeking behaviors assessments on days 3 and 21. Immediately after this last drug-seeking assessment, rats were sacrificed, and their brains were prepared for electrophysiological assessment (whole-cell patch-clamping). The firing activity of mPFC pyramidal neurons was assessed with perfusion of human plasma isolated bulk IgG antibodies (in μg/mL: 2.5, 5) from severe or mild COVID-19 patients. We found that both HIV-1 Tg and non-Tg rats displayed similar drug-taking behaviors. Additionally, while drug-seeking behaviors were attenuated, they persisted, indicating an enduring Coc-induced neuroplasticity associated with hyperactivity and altered membrane properties of mPFC neurons. We also found that IgG antibodies isolated from severe COVID-19 patients significantly enhanced firing of mPFC neurons in SAL-yoked rats and worsened neuronal hyperactivity in Coc-SA rats. Moreover, our pilot data also suggests that IgGs isolated from mild COVID-19 patients induced no change in neuron firing. This novel finding, in combination with our earlier study, suggests that while SARS-CoV-2 spike protein abnormally increases mPFC neuron activity, SARS-CoV-2-evoked bulk IgG could also potentiate mPFC neuron overactivation, which could cause injury and even death of neurons in the brain. This potential mechanism may underlie the neurocognitive deficits seen in COVID-19 patients and could worsen those in the synergistic epidemics (syndemic) of COVID-19, neuroHIV, and CUD.

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Poster

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Title: Lincrna nostrill modulates antiviral response to tmev infection in neurons

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Abstract: Viral infection can cause a neuroinflammatory response leading to neuronal damage and an increased risk of neurodegenerative disease in humans. Neurons and microglial cells drive an antiviral response to effectively clear virus or ineffectively clear virus and promote neurodegeneration. Previous work in our lab shows that viral infection of microglia with Theiler Murine's Encephalomyelitis Virus (TMEV) upregulates an NFkB-dependent noncoding RNA Nostrill. Nostrill regulates Interferon response factor 7 (*Irf7*) and Type 1 interferon (*Ifnα/β*) gene

transcription in microglia *in vitro*. In a TMEV mouse model system that models viral-induced neurodegenerative disease, neurons are infected before microglia. Whether neurons upregulate Nostrill to mount an antiviral response is not known. *In vivo* and *in vitro* TMEV viral infection models were used to investigate whether Nostrill is important for antiviral responses in neurons. The *in vivo* model system examined Nostrill expression in mice susceptible to (FVB/nJ) and mice resistant (C57Bl6) to TMEV infectious degenerative disease. Human SHSY5Y neuronal cells were for *in vitro* mechanistic studies. RT-qPCR analyses of the brain tissue of FVB/nJ mice 11 days post viral infection, showed that Nostrill is significantly upregulated ~3fold ($p=0.02$, $N\geq4$) in TMEV infected mice compared to uninfected mice. In TMEV infected FVB/nJ mice, *iNos* and *Ifnγ* are upregulated ~2fold ($p=0.04$, $N\geq4$) and ~10fold ($p<0.0001$, $N\geq4$) compared to uninfected FVB/nJ mice, respectively. *Ifnα*/*Ifnβ* are significantly decreased ~0.6fold ($p=0.01$, $N\geq4$). Significant changes in Nostrill, *iNos, Ifnγ, Ifnα/Ifnβ* expression are not observed in resistant C57Bl6 mice. *In situ* analyses demonstrate higher Nostrill expression in neurons of FVB/nJ mice compared to C57Bl6 mice. *In vitro* data show that Nostrill orthologs are upregulated in SHSY5Y neurons in a dose- and time-dependent manner following TMEV infection. These data suggest that the lincRNA Nostrill is differentially expressed in the brain and neurons of mice that develop virally induced neurodegenerative disease. Future studies will further investigate the role of Nostrill expression to modulate neuronal immune responses during antiviral immunity.

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Poster

PSTR335: Neuroinflammation: HIV and Infections

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: EENT Foundation

Title: Elv-n34 or rvd6-isomer counteracts damaging astrocyte phenotypes promoted by long covid

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Abstract: Neurodegenerative diseases induce astrocyte phenotypes that trigger inflammation and cell damage. This cell induction also takes place in post-acute neurological syndrome from SARS-CoV-2 infection. The **purpose** of this study is to determine the effects of the molecules secreted by human nasal epithelial cells infected with SARS-CoV-2 Omicron BA.5 variant on human astrocytes and whether elovanoid 34 (ELV-34) and resolvin D6 (RvD6) can counteract this activity. **Methods**: Human nasal epithelial cells from 50-year-old healthy donors were infected with Omicron BA.5 for one hour. The cells were treated with 500nM ELV-34, RVD6, or vehicle before and after the infection. The exudate (conditioned media) was used to induce human astrocytes in culture. Two of the identified factors that changed the phenotype of the astrocytes, were used to treat intranasally male and female mice, to mimic the virus nasal infection. **Results**: we found that the secretome from Omicron BA.5 infected human nasal epithelial or human lung cells induced the activation of human astrocytes to a reactive pro-inflammatory phenotype as defined by nuclear translocation of NF-kB/p65. Remarkably, the secretome from these cells incubated with Elovanoid (ELV)- N34 or Resolvin D6 (RvD6)-isomer (500nM) did not trigger the formation of reactive astrocytes. One of the factors involved is CXCL1, secreted by Omicron BA.5-infected nasal epithelial cells. So, when CXCL1 was administered intranasally to mice along with Interferon type I, the internalization of fluorescein indicated a permeabilization of the neurovascular unit. The joint administration of CXCL1 and IFN-I also induced the activation of astrocytes noticeable by the increased GFAP expression in glial cells. **Conclusions**: Astrocytes are close to this barrier and contribute to restricting the access of damaging molecules to the brain parenchyma. Together, these results point to a specific way of entry of chemokines and cytokines as part of the secretome from infected cells that may play a role in long-term COVID brain sequelae.

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Poster

PSTR335: Neuroinflammation: HIV and Infections

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Title: Sting signaling protects against central nervous system invasion in animal models of Listeria monocytogenes

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Abstract: *Listeria monocytogenes* (*L.m.*) is a bacterial pathogen responsible for the foodborne illness listeriosis. *L.m.* is among the most common causes of bacterial meningitis and/or meningoencephalitis among newborns and immunocompromised individuals, and once *L.m.* crosses into the central nervous system (CNS), lethality exceeds 50%, even with aggressive medical treatment. The mechanisms that opportunistic bacterial pathogens such as *L.m.* utilize to gain access to the central nervous system (CNS) are poorly understood. We have previously demonstrated that the innate immune regulator STING is highly expressed by pain-sensing nociceptors in peripheral sensory ganglia and in spinal microglia. In this study, we sought to determine how STING signaling in peripheral sensory neurons and/or microglia impacts CNS invasion and survival outcomes in a mouse model of L.m.-induced infection. To this end, we administered various titers of *L.m.* (10^5 to 10^7 CFU/ml, *i.p.*) to male and female mice and examined bacterial load in peripheral and central nervous system tissues (trigeminal ganglia, dorsal root ganglia, spinal cord, and brain). We also measured survival outcomes as well as short and long-term behavioral consequences in survivors post-infection.
In wildtype C57BL/6J mice, females exhibited lower probability of survival, increased spontaneous pain behaviors, and reduced locomotor activity when compared with male mice. *L.m.* led to time-dependent increases in bacterial load in peripheral sensory ganglia, spinal cord, and brain tissue. Interestingly, intrathecal administration of very low doses of small molecule STING agonists reduced bacterial load in the CNS and substantially increased survival in males but not females. Given that intrathecal drug administration activates cell types in both the primary sensory ganglia and in the spinal cord, we utilized cell ablation methods to determine the cellular mechanism(s) underlying this effect. Nociceptor ablation using the TRPV1 super-agonist resiniferatoxin (RTX) led to heightened sickness behaviors in both sexes but did not significantly alter survival outcomes, whereas microglial ablation led to increased mortality and morbidity in male but not female mice. Overall, these data suggest that STING pathway agonists may be a promising therapeutic strategy to mitigate morbidity and mortality in L.m.-induced sepsis in males. Ongoing work is aimed at identifying the cell type(s) responsible for these protective effects. We are also exploring the generalizability of these findings in other infection models.

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Poster

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NS060632
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Title: Astrocyte Dysfunction in NeuroHIV and Cocaine Abuse

Authors: *T. KREKO-PIERCE, L. AL-HARTHI, R. M. VOIGT, X.-T. HU;
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Abstract: Despite the ability of combination antiretroviral therapy (cART) to dramatically suppress viremia, the brain continues to be an HIV reservoir. It has been estimated that approximately 30−60% of infected individuals on the cART regimen go on to develop varying degrees of neurological dysfunction, collectively termed HIV-associated neurocognitive disorders (HAND, a.k.a. neuroAIDS/neuroHIV). Drug abuse, such as cocaine (Coc) use, is a prominent comorbidity and contributor to HIV-1 infection. It is common among people living with HIV-1 (PLWH, ~50%) reporting a current or past drug abuse history. The prefrontal cortex (PFC) is dysregulated in neuroAIDS and Coc addiction, and the comorbid condition results in greater impairment of PFC-mediated cognitive tasks. Our previous work reveals that the pyramidal neurons in the medial PFC (mPFC) of a rat model of NeuroHIV, as well as those chronically exposed to Coc, exhibit an abnormal increase of excitability. Furthermore, we also demonstrated that the combination of neuroHIV and chronic Coc self-administration (Coc-SA) causes even greater hyperactivity of these neurons; however, the mechanism that drives hyperexcitability in these conditions is not fully understood. This represents a major knowledge gap as mPFC pyramidal neurons are important mediators of brain function and behaviors that are disrupted in neuroAIDS and by chronic Coc exposure. The mechanisms that underlie the hyperexcitability and the enhanced neuropathology in these conditions are unclear. Astrocytes, the most abundant glial cells in the CNS, play essential roles in maintaining brain homeostasis, including the regulation of neuronal excitability. This suggests that astrocytes may be particularly important in the context of HIV infection and Coc-SA. However, the specific role of astrocytes in HIV- and Coc-mediated neuronal excitability remains unknown. Our rat and human brain tissue data support the hypothesis that astrocyte dysfunction is a putative mechanism deteriorating the mPFC hyperactivity observed in neuroHIV and Coc addiction. Specifically, we demonstrate changes in the expression of the potassium channel $K_{ir}4.1$, the glutamate transporter GLT-1, and the gap junction protein connexin-43 (Cx-43) in astrocytes, which may contribute to the dysregulation of neuronal excitability in these conditions. These findings provide novel insights into the potential role of astrocytes in the neuropathogenesis associated with neuroHIV and Coc abuse and may guide future research aimed at developing targeted interventions to mitigate the neurological consequences of these conditions.

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Poster

PSTR335: Neuroinflammation: HIV and Infections

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LMGC is the recipient of a CAPES doctoral scholarship

Title: Vitamin B12 as an epidrug for regulating peripheral blood biomarkers in long COVID-associated visuoconstructive deficit

Authors: L. M. G. CASSIANO[1,2], J. J. DE PAULA[3], D. V. ROSA[3], D. M. MIRANDA[3], M. A. ROMANO-SILVA[3], ***R. S. COIMBRA**[1];
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Abstract: Approximately four months after recovering from a mild COVID-19 infection, around 25% of individuals developed visuoconstructive deficit (VCD), which was found to be correlated with an increase in peripheral immune markers and alterations in structural and metabolic brain imaging. Recently, it has been demonstrated that supplemental vitamin B12 regulates hyperinflammation during moderate and severe COVID-19 through methyl-dependent epigenetic mechanisms. Herein, whole peripheral blood cultures were produced using samples obtained from patients with confirmed persistent VCD, and controls without impairment, between 10 and 16 months after mild COVID-19. This experimental model was used to assess the leukocyte expression patterns of 11 biomarkers previously associated with VCD in long COVID and explore the potential of pharmacological B12 in regulating these genes. The results showed that patients with persistent VCD displayed continued upregulation of *CCL11* and *LIF* compared to controls. It is worth noting that elevated serum levels of CCL11 have been previously linked to age-related neurodegenerative diseases. Notably, the addition of 1 nM of vitamin B12 to blood cultures from individuals with VCD normalized the mRNA levels of *CCL11*, upregulated the neuroprotective *HGF*, and, to a lesser extent, downregulated *CSF2* and *CXCL10*. There was an inverse correlation observed between *CCL11* mRNA levels and methylation levels of specific cytosines in its promoter region. These findings underscore the significance of systemic inflammation in persistent VCD associated with long COVID. Moreover, the study provides evidence suggesting that B12, acting as an epidrug, shows promise as a therapeutic approach for addressing this cognitive impairment.

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Poster

PSTR335: Neuroinflammation: HIV and Infections

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

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Brain Lung Interaction Brazil-Canada Student Exchange Grant from the Department of Foreign Affairs, Trade and Development Canada
UofT Pitts Research Chair in Acute care and Emergency Medicine

Title: Extracellular vesicles derived from clonally-expanded immortalized mesenchymal stromal cells reduce neuroinflammation in pre-clinical sepsis

Authors: *M. B. DA SILVA[1], A. EKTESABI[2], Y. MOULOUD[3], J. TSOPORIS[2], C. VASWANI[2,4], S. IZHAR[2], T. MARON-GUTIERREZ[5], B. GIEBEL[3], C. C DOS SANTOS[6,7,8]; [1]Oswaldo Cruz Institute- Fiocruz, Rio de Janeiro, Brazil; [2]Keenan Res. Ctr.for Biomed. Science, St. Michael's Hospital-UofT, Toronto, ON, Canada; [3]Inst. for Transfusion Medicine, Univ. Hosp. Essen, Univ. of Duisburg-Essen, Essen, Germany; [4]Dept. of Physiology, Temerty Fac. of Medicine-UofT, Toronto, ON, Canada; [5]Oswaldo Cruz Inst. Fiocruz, Rio de Janeiro, Brazil;, Rio de Janeiro, Brazil; [6]Keenan Res. Ctr.for Biomed. Science, St. Michael's Hospital-Univ. of Toronto, Toronto, ON, Canada; [7]Dept. of Physiology, Temerty Fac. of Medicine, UofT, Toronto, ON, Canada; [8]Interdepartmental Div. of Critical Care, St Michael's Hospital, UofT, Toronto, ON, Canada

Abstract: Sepsis is an exacerbated host response against an infection. Sepsis-associated encephalopathies (SAE) are neurological complications which occur during or after sepsis events. Currently, there is no treatment available for SAE-induced neurological damage. Therefore, it is necessary to investigate new therapeutic approaches. Mesenchymal stromal cells (MSCs) have a well-established immunomodulatory capacity. Our group demonstrated beneficial effects of MSC therapy in reducing neuroinflammation and cognitive damage caused by SAE, further, MSCs seems act in a paracrine way. Extracellular vesicles (EVs) are lipid bilayer-delimited particles carrying proteins, nucleic acids, and lipids released by cells. EVs from MSCs (MSC-EVs) are promising candidates for different types of therapy due to their capacity to carry and deliver mediators from MSCs. Our aim was to evaluate the effects of MSC-EV therapy in an experimental model of sepsis. Our readouts were survival, peripheral inflammation and neuroinflammation. For this, male adult C57Bl/06 mice underwent surgery for sepsis induction. Six hours after surgery, mice were treated with MSC-EVs intravenously. MSC-EV therapy improved survival rates 72h after surgery. At the same timepoint MSC-EV therapy reduced peripheral inflammation. In the cortex and hippocampus, also at 72h, MSC-EV therapy led to a reduction in astrogliosis and microglial activation. Despite the reduction in neuroinflammation, we did not observe any changes in the local synthesis of cytokines or blood-brain barrier integrity. In cultured microglial-BV2 cells, stimulated with LPS, MSC-EVs reduced the expression of IL-6 and IL-1b, suggesting an anti-inflammatory effect. Finally, this effect could be blocked by Dynasore—an inhibitor of clathrin/dynamin-mediated endocytosis. Thus, we can conclude that, in our model, a single dose-therapy with MSC-EVs reduced peripheral inflammation, neuroinflammation, and improved survival rates. Further, using an in vitro model,

we show that these EV-mediated effects are likely dependent on endocytosis, highlighting the potential of EVs as tissue-specific targeted therapies.

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Poster

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Topic: C.10. Brain Injury and Trauma

Support: Camden Health Research Initiative to DAF and RJB

Title: An analysis of differential gene expression in peripheral nerve and muscle utilizing RNA sequencing after polyethylene glycol nerve fusion in a rat sciatic nerve injury model.

Authors: *R. J. BUONO[1], D. A. FULLER[2], S. N. WEISS[1], Y. LIU[3], H. HAKONARSON[3]; [1]Cooper Med. Sch. of Rowan Univ., Camden, NJ; [2]Orthopedic Surgery, Cooper Univ. Hosp., Camden, NJ; [3]Ctr. for Applied Genomics, The Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: Application of polyethylene glycol (PEG) to a peripheral nerve injury at the time of primary neurorrhaphy is thought to prevent Wallerian degeneration via direct axolemma fusion. The molecular mechanisms of nerve fusion and recovery are unclear. Our study tested the hypothesis that PEG alters gene expression in neural and muscular environments as part of its restorative properties. Lewis rats underwent unilateral sciatic nerve transection with immediate primary repair. Subjects were randomly assigned to receive either PEG treatment or standard repair at the time of neurorrhaphy. Samples of sciatic nerve distal to the injury and tibialis muscle at the site of innervation were harvested at 24 hours and 4 weeks postoperatively. Total RNA sequencing and subsequent bioinformatics analyses were used to identify significant differences in differentially expressed genes (DEGs) and their related biological pathways ($p>0.05$) in PEG-treated subjects compared to non-PEG controls. No significant DEGs were identified in PEG-treated sciatic nerve compared to controls after 24 hours, but 1,480 DEGs were identified in PEG-treated tibialis compared to controls. At 4 weeks, 918 DEGs were identified in PEG-treated sciatic nerve, whereas only 3 DEGs remained in PEG-treated tibialis compared to controls. DEGs in sciatic were mostly upregulated (79%) and enriched in pathways present during nervous system development and growth, whereas DEGs in muscle were mostly downregulated (77%) and related to inflammation and tissue repair. Our findings indicate that PEG application during primary neurorrhaphy leads to significant differential gene regulation in the neural and muscular environment that is associated with improved functional recovery in animals treated with PEG compared to sham non-PEG controls. A detailed understanding of key

molecules underlying PEG function in recovery after peripheral nerve repair may facilitate amplification of PEG effects through systemic or focal treatments at the time of neurotmesis.

Disclosures: R.J. Buono: None. **D.A. fuller:** None. **S.N. Weiss:** None. **Y. Liu:** None. **H. Hakonarson:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.02/C143

Topic: D.02. Somatosensation – Touch

Support: SAMSUNG Grant, SEFC-MA2302-05

Title: Axonal Localization of Ribosome Protein mRNA is Managed by NonO to Promote Local Translation in Regenerating Axons.

Authors: *Y. JEON[1], Y. OH[1], E. JANG[1], H. JIN[1], J. SHIN[2], Y. CHO[1];
[1]Daegu Gyeongbuk Inst. of Sci. & Technol., DGIST, Daegu, Korea, Republic of; [2]Dept. of Mol. Neurosci., Dong-A Univ., Busan, Korea, Republic of

Abstract: Axonal RNA translation is essential for protein supply during nerve regeneration after nerve injury. Non-POU domain-containing octamer-binding (NonO), a nuclear RNA-binding protein also known as p54nrb, assembles paraspeckles in the nucleus, regulating nuclear export and translation of target mRNA. NonO is abundant in sensory neuron cell bodies in the dorsal root ganglion (DRG). We found that NonO binds to a group of mRNAs for axon regeneration and elongation, with enriched interaction with ribosome-coding mRNAs, which are highly expressed in axons. This result suggests a previously unknown role of NonO in axonal mRNA regulation and translation. We found that NonO depletion caused a significant increase in ribosome protein mRNA levels in axons, leading to a quantitative increase in their protein levels. To determine whether axonal translation consequently increases after NonO depletion, we performed puromycin labeling assays and observed increased translation in regenerating axons by NonO knockdown. Consistent with the importance of axonal translation during regeneration, NonO knockout mice showed a high axon regeneration potential in injured mouse sciatic nerves and adult DRG neurons. Knocking down NonO could partially rescue axonal outgrowth suppressed by the treatment with the translation inhibitor cycloheximide. Taken together, we demonstrate that ribosome-coding mRNA are regulated by the nuclear RNA-binding protein NonO after axonal injury and NonO depletion can enhance axon regeneration through increased axonal translation.

Disclosures: Y. Jeon: None. **Y. Oh:** None. **E. Jang:** None. **H. Jin:** None. **J. Shin:** None. **Y. Cho:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.03/C144

Topic: C.10. Brain Injury and Trauma

Support: R21NS111334-01

Title: The effect of Schwann cell-derived exosome treatment in various models of peripheral nerve injury within the rat

Authors: *E. SCHAEFFER, E. L. ERRANTE, A. KHALAFALLAH, A. KLOEHN, A. D. LEVI, S. BURKS;
Univ. of Miami, Miami, FL

Abstract: Peripheral nerve damage is one of the most common injuries amongst trauma cases which can result in debilitating symptoms, including paralysis. Treatments for the most severe cases of peripheral neve injury (PNI) often subject patients to substantial side effects including compromised sensory function, pain from harvesting of donor graft material, donor source availability, and long-term immunosuppressants with graft-rejection potential in cases of cellular allografts. Cellular-based therapies using extracellular vesicles derived from Schwann cells (SC) have demonstrated some clinical promise for PNI due to their neuroregenerative potential and ease of delivery. Although recent literature has found success in exosome-based intervention following PNI, the treatment efficacy has yet to be compared following various injury and severity models. Therefore, the currently study investigated SC-derived exosome treatment in sciatic nerve crush vs. large-gap, compared to the gold standard treatment, autograft, and nerve transection. Specifically, adult male Fischer rats received a unilateral sciatic nerve injury and exosome therapy, depending on group membership: 13mm reverse autograft, 13mm nerve gap + nerve guidance channel loaded with SC-derived exosomes, nerve crush + SC-derived exosomes, or transection. Sensory and motor function was evaluated longitudinally across 12-weeks. Preliminary results suggest longitudinal changes for functional outcome measures across groups. Results from the proposed research are implicated in the curation of alternative treatments for PNI, without the costly side effects of current therapeutic options (e.g., donor source availability, immunogenicity, and graft rejection). Future research should evaluate the efficacy of SC-derived exosomal therapy in other PNI models (e.g., chronic compression) and other nervous system injuries, including that of the brain and spinal cord.

Disclosures: E. Schaeffer: None. **E.L. Errante:** None. **A. Khalafallah:** None. **A. Kloehn:** None. **A.D. Levi:** None. **S. Burks:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.04/C145

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R01 NS-128086

Title: Successful Polyethylene Glycol Fusion Repair of Traumatic Ablation Peripheral Nerve Injuries Using Stored Nerve Allografts After a Time Delay

Authors: *L. ZHOU[1], C. Z. YANG[1], A. M. SCHAFER[1], A. N. OLIVAREZ[1], G. PERIYASAMY[1], A. AGARWAL[1], V. GOKHALE[1], R. SOOD[1], H. GARCIA[1], J. S. BUSHMAN[2], G. D. BITTNER[1];
[1]Inst. For Neurosci., Univ. of Texas at Austin, Austin, TX; [2]Pharmaceut. Sci., Univ. of Wyoming, Laramie, WY

Abstract: Polyethylene glycol fusion (PEG-fusion) repair of traumatic transection and ablation (segmental-loss) peripheral nerve injuries (PNIs) (1) immediately re-establishes morphological and electrophysiological continuity across the lesion site, (2) prevents Wallerian degeneration of successfully PEG-fused axons, (3) maintains innervation of many neuromuscular junctions, and (4) results in faster and better motor and sensory recovery in rats than other current repair protocols. Importantly, PEG-fusion repair of ablation PNIs using viable peripheral nerve allografts (VPNAs) containing viable axons does not require tissue-matching or immunosuppression. These results challenge the clinical use of nerve *autografts*, which is the "gold standard" for ablation PNI repairs but produces donor site morbidity and often mismatching of host/donor nerve diameters and/or sensory/motor modalities. We previously demonstrated some optimal VPNA storage conditions that maintained the viability of many axons for up to 9d, as evident by *ex vivo* compound action potentials and axon morphology. We now show successful PEG-fusion repair with (Group 1) stored VPNAs and/or (Group 2) delayed repairs. Our pilot cohorts of Lewis rats were subjected to repairs using 1d, 2d, 3d, and 5d of stored Sprague Dawley VPNAs in Group 1 and repairs following 1d delay in Group 2. Our data demonstrate immediate restoration of axon continuity, preservation of many axons, changes in immune infiltration, and better behavioral recovery compared to Negative Controls not treated with PEG. There are five clinical trials to assess PEG-fusion repair of transection PNIs (just entering phase III) and ablation PNIs using nerve *autografts*. Our data provide strong evidence and incentive to promote the clinical translation of PEG-fusion repair of ablation PNIs using VPNAs and establishing donor VPNA tissue banks.

Disclosures: L. Zhou: None. **C.Z. Yang:** None. **A.M. Schafer:** None. **A.N. Olivarez:** None. **G. Periyasamy:** None. **A. Agarwal:** None. **V. Gokhale:** None. **R. Sood:** None. **H. Garcia:** None. **J.S. Bushman:** None. **G.D. Bittner:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.05/C146

Topic: C.10. Brain Injury and Trauma

Title: Combined cranial and peripheral nerve stimulation improves functional recovery after peripheral nerve injury

Authors: S. EFTEKARI[1], D. DONNELLY[1], W. ZENG[1], S. POORE[1], A. M. DINGLE[1], ***A. J. SUMINSKI**[2];
[1]Surgery, [2]Neurolog. Surgery, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Peripheral nerve reinnervation following nerve injury is often a slow and incomplete process, resulting in significant morbidity and permanent loss of function of the injured extremity. Prior studies have shown the efficacy of electrical stimulation to accelerate the recovery of both motor and sensory neurons in peripheral nerve injury models. Moreover, separate investigations have also shown the use of closed-loop cranial nerve stimulation to improve the neuroplasticity of the motor cortex, improving functional outcomes. However, no study has investigated the synergistic effects of the interventions. This investigation quantifies the efficacy of both intraoperative electrical stimulation and trigeminal nerve stimulation on motor and sensory functional recovery in a rat peripheral nerve injury model. Twelve Lewis rats were trained in a reach-to-grasp task for a food reward using their right forelimb in the MotoTrak training system. Baseline sensory data was also retrieved using a Von Frey monofilament test. All rats underwent surgical transection of the median and ulnar nerve of their right forelimb, followed by one hour of intraoperative electrical stimulation. Adjuvant trigeminal nerve stimulation was completed via supraorbital headcap electrodes. Force and sensory data were compared to cohorts of sham surgery (no nerve transection), brief intraoperative electrical stimulation, adjuvant trigeminal nerve stimulation, and a no-stimulation group. The combined cohort of rodents were able to recover to their pre-injury motor function by the third week of rehabilitation, faster than either of the singular electrical stimulation cohorts assessed previously. Moreover, the combined stimulation cohort's functional sensory data demonstrated no change compared to their pre-injury baseline, indicating a full functional recovery prior to the first data timepoint.

Disclosures: S. Eftekari: None. **D. Donnelly:** None. **W. Zeng:** None. **S. Poore:** None. **A.M. Dingle:** None. **A.J. Suminski:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.06/C147

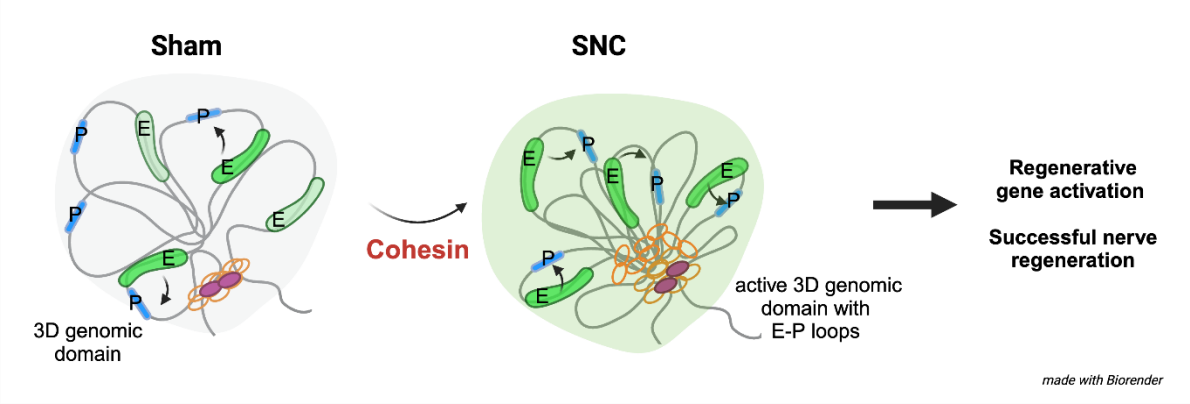
Topic: C.10. Brain Injury and Trauma

Support: Medical Research Council
National Institute of General Medical Sciences
Start up
Wings For Life
The Rosetrees Trust
National Institute for Health Research

Title: Three-dimensional chromatin looping is required for nerve regeneration after injury

Authors: *I. PALMISANO[1,2], T. LIU[3], W. GAO[2], L. ZHOU[2], M. MERKENSCHLAGER[4], F. MUELLER[5], J. S. CHADWICK[2], R. TOSCANO RIVALTA[2], G. KONG[2], J. KING[4], E. AL-JIBURY[2], B. COLLISON[1], A. CARLINO[1], E. DE VITIS[1], Y. YAN[2], S. GONGALA[2], F. DE VIRGILIIS[2], Z. WANG[3], S. DI GIOVANNI[2];
[1]Ohio State Univ., Columbus, OH; [2]Imperial Col. London, London, United Kingdom; [3]Univ. of Miami, Miami, FL; [4]MRC London Inst. of Med. Sci., London, United Kingdom; [5]Imperial college London, London, United Kingdom

Abstract: Axonal regeneration after injury relies on coordinated changes in expression of hundreds of functionally connected regenerative genes. Gene expression changes are regulated within three-dimensional (3D) genomic domains, called **topologically associating domains** (TADs), generated by the protein complex **cohesin**. Within TADs, cohesin generates chromatin loops that allow functional interactions between enhancers and target gene promoters, critical for transcriptional activation. Despite the crucial role of 3D genome architecture in gene regulation, whether it plays a role in axonal regeneration after injury remains elusive. To address this question, we performed Hi-C, promoter-Hi-C, CUT&Tag for H3K27ac and RNA-seq in purified dorsal root ganglia (DRG) sensory neurons from wildtype and cohesin conditionally depleted mice 3 days after sciatic nerve crush. We found that cohesin preferentially regulates genes involved in axonal regeneration. Cohesin was required for the activation of regenerative genes via formation of long-range chromatin loops connecting their promoters to distal enhancers. Loss of cohesin resulted in failure in activation of regenerative gene networks and in severely impaired nerve regeneration. These data reveal a central role for 3D genome architecture in the control of regenerative gene expression and identify **cohesin as a novel regulator of nerve regeneration**. One of the reasons of the regenerative failure after spinal cord injury (SCI) is that regenerative gene expression is not sustained over time. Preliminary data show that after SCI regenerative genes display a lower frequency of chromatin interactions. This suggests that the **regenerative deficit after SCI might result from the failure of cohesin to establish stable chromatin interactions at regenerative genes.** Promisingly, overexpression of the cohesin loading factor -Nipped-B-like protein- was sufficient to enhance regenerative growth of DRG sensory neurons in vitro on both permissive and non-permissive substrate.



Disclosures: I. Palmisano: None. **T. Liu:** None. **W. Gao:** None. **L. Zhou:** None. **M. Merkenschlager:** None. **F. Mueller:** None. **J.S. Chadwick:** None. **R. Toscano Rivalta:** None. **G. Kong:** None. **J. King:** None. **E. Al-jibury:** None. **B. Collison:** None. **A. Carlino:** None. **E. De Vitis:** None. **Y. yan:** None. **S. Gongala:** None. **F. De Virgiliis:** None. **Z. Wang:** None. **S. Di Giovanni:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.07/C148

Topic: C.10. Brain Injury and Trauma

Support: Canadian Institutes of Health Research

Title: Wallerian degeneration across the lifespan in female and male mice following injury to the peripheral nervous system

Authors: *P. EDALAT[1,2], S. S. OUSMAN[3];
[1]Clin. Neurosci., Univ. of Calgary, Calgary, AB, Canada; [2]Hotchkiss Brain Institute, Calgary, AB, Canada; [3]Clin. Neurosciences and Cell Biol. & Anat., Hotchkiss Brain Inst., Univ. of Calgary, Calgary, AB, Canada

Abstract: Regeneration of peripheral nervous system (PNS) neurons after nerve crush, stretch, or degenerative damage in humans is often incomplete, leading to motor and sensory deficits such as movement disorders and neuropathic pain. Moreover, PNS regeneration and functional recovery are worse with advanced age. Since males disproportionately sustain PNS injuries, we are investigating if Wallerian degeneration events are similar or different in the PNS between the two sexes over the lifespan. To this end, a crush injury was performed on the right sciatic nerve of 1-, 3-, 6-, 12- and 18-month-old female and male 129SVE mice. The left sciatic nerve served as a sham control. To monitor for early and late Wallerian degeneration processes, nerve segments distal to the injury site were harvested at 7- and 28-days post-injury, frozen and ten microns thick sections stained for myelinating Schwann cells [S100beta+myelin protein zero

(P0)+], and non-myelinating Schwann cells [S100beta+glial fibrillary acidic protein (GFAP)+]. Thus far, we have found that the number of S100+P0+ and S100+GFAP+ profiles is similar between 3- and 12-month-old female and male injured mice. Further analyses will include older animals (18-month-old). We will also assess the number of pro- and anti-inflammatory macrophages and their phagocytic ability (colocalization with P0), the expression of cell adhesion molecules by Schwann cells, Schwann cell cholesterol level and myelinating capacity, as well as the number of regenerating axons in injured nerves from 1- to 18-month-old mice. Altogether, we will obtain a detailed analysis of Wallerian degeneration events between young and old female and male mice after PNS injury.

Disclosures: P. Edalat: None. **S.S. Ousman:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.08/C149

Topic: C.10. Brain Injury and Trauma

Support: SAMSUNG Grant, SEFC-MA2302-05

Title: Single nucleotide differences in Gpr151 functional RNA 5'UTR sequence changes axon regenerative potential in CAST/EiJ mice

Authors: *E. JANG[1,2], Y. LEE[2], Y. CHO[2];
[1]Brain Sci., DGIST, Daegu, Korea, Republic of; [2]DGIST, Daegu, Korea, Republic of

Abstract: For successful nerve regeneration following injury, neurons undergo dynamic transcriptomic changes. *Gpr151* is one of the injury-responsive genes and has a significant role at the RNA level rather than the protein level. Our previous research has demonstrated that the 5’UTR RNA sequence of Gpr151 contributes to axon regeneration by direct binding with CSDE1 protein and altering its coordinating RNA pool. Here, we discovered a distinct SNP within this functional *Gpr151* RNA in CAST/EiJ mice, known for their high neuronal regenerative potential, resulting in structural differences. The 5’UTR sequence of Gpr151 in CAST/EiJ mice significantly enhances axon regeneration compared to that of C57BL/6 mice. Additionally, differences are noted in the respective binding proteins. Our studies aim to deepen the understanding of the functional RNA and the impact of its SNP.

Disclosures: E. Jang: None. **Y. Lee:** None. **Y. Cho:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.09/C150

Topic: C.10. Brain Injury and Trauma

Support: SAMSUNG Grant, SEFC-MA2302-05

Title: Investigation of an RNA binding protein CSDE1's role for mitochondria functions

Authors: *H. JIN[1], E. JANG[2], Y. CHO[1];
[2]Brain Sci., [1]DGIST, Daegu, Korea, Republic of

Abstract: CSDE1 is a cytoplasmic RNA binding protein regulating target mRNAs' translation and stability. Additionally, mitochondria perform crucial functions beyond cellular energy production, contributing to the survival, maintenance, and regeneration of neural function. To investigate the RNA pool binding to CSDE1 involved in regeneration, CSDE1-IP Sequencing was conducted on injured or uninjured Dorsal Root Ganglion (DRG) tissues. CSDE1 was found to be associated with host cell-derived and mitochondria-derived mitochondria-associated RNA, including Electron Transport Chain protein coding RNA. Furthermore, although contamination from other organelles such as lysosomes cannot be completely excluded, the presence of CSDE1 in isolated mitochondrial fractions was confirmed through biochemical fractionation. This suggests that the cytoplasmic RNA binding protein CSDE1 may have a role in regulating mitochondrial functions. Based on these findings, our aim is to explore a novel principle governing the dynamic regulation between RNA, RBPs, and mitochondria in neurons, and further investigate their impact on axon regeneration.

Disclosures: H. Jin: None. **E. Jang:** None. **Y. Cho:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.10/C151

Topic: C.10. Brain Injury and Trauma

Support: Adelson Medical Research Foundation grant (DHG, RJG)
F31 NS135919-01 (HH)

Title: The Role of Hif1a Regulated Glycolytic Flux in Macrophages for Peripheral Nervous System Regeneration and Development of Neuropathic Pain

Authors: *M. ATHAIYA[1], H. HAFNER[2], X.-F. ZHAO[3], R. KAWAGUCHI[4], D. H. GESCHWIND[5], R. J. GIGER[6];
[1]Cell and Developmental Biol., Univ. of Michigan, Ann Arbor, MI; [2]Univ. of Michigan, Ann Arbor, MI; [3]Cell and Developmental Biol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI;

[4]Univ. of California, Los Angeles, CA; [5]UCLA, Los Angeles, CA; [6]Neurology/Cell and Developmental Biol., Univ. of Mchigan, Ann Arbor, MI

Abstract: The most prevalent types of nervous tissue injury involve traumatic lesions to the peripheral nervous system (PNS). It has long been recognized that upon PNS injury, the immune system plays a pivotal role in nerve fiber degeneration, axon regeneration, and the development of chronic pain. Recent advancements in longitudinal single-cell RNA-sequencing have illuminated the molecular response of mice to sciatic nerve crush (SNC) at single-cell resolution. Reminiscent of injured non-neural tissues, monocytes and macrophages (Mo/Mac) that accumulate in the injured nerve undergo profound metabolic reprogramming within the first week post-SNC. Upon nerve entry, Mo/Mac rapidly upregulate glycolytic flux, and there is a simultaneous reduction in mitochondrial oxidative phosphorylation (OXPHOS). Starting around 3 days post-SNC, Mo/Mac downregulate glycolysis and increase OXPHOS. The transcriptional regulator Hypoxia-Inducible Factor 1a (Hif1a), a master regulator of glycolytic enzymes, is strongly upregulated in Mo/Mac that enter the injured nerve, prompting investigations of the role of Hif1a, and thereby glycolysis, in the injured sciatic nerve. We found that conditional ablation of Hif1a in Mo/Mac [*Hif1a(fl/fl);LysM-cre*, hereafter Hif1a cKO], results in reduced regeneration of sensory and motor axons. Longitudinal behavioral assessments at 35, 42, and 49 days post-SNC unveiled the onset of neuropathic pain in Hif1a cKO mice. To validate Hif1a ablation and to study the impact on immune metabolism, we generated bone marrow-derived macrophages (BMDMs) from wildtype (WT) and Hif1a cKO mice. qRT-PCR for Hif1a transcript confirmed highly efficient gene ablation. To assess metabolic reprogramming, BMDMs were treated with LPS, and glycolytic flux and mitochondrial activity were assessed using Seahorse XF. Notably, Seahorse analysis demonstrated a significant decrease in lactate export and increased mitochondrial activity in Hif1a cKO BMDMs compared to parallel processed WT BMDMs. This confirms that metabolic reprogramming is indeed impaired in Hif1a cKO mice. Ongoing investigations focus on Mo/Mac metabolic reprogramming and phenotype in the injured sciatic nerve of Hif1a cKO mice, and investigation of mechanisms that may contribute to alteration in axon regeneration and pain sensation. A better understanding of Mo/Mac metabolic reprogramming in the injured PNS can provide new therapeutic opportunities to influence axon regeneration and mitigate neuropathic pain. Additional Authors: C. Johnson (CDB), D. Sutton, C. Lyssiotis (MIP) University of Michigan

Disclosures: M. Athaiya: None. **H. Hafner:** None. **X. Zhao:** None. **R. Kawaguchi:** None. **D.H. Geschwind:** None. **R.J. Giger:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.11/C152

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant F31 NS135919-01 (HH)
Adelson Medical Research Foundation Grant (RJG)

Title: The role of bone marrow derived macrophages in peripheral nervous system injury

Authors: *H. HAFNER[1], X.-F. ZHAO[2], D. WILBORN[3], M. ATHAIYA[1,4], L. SCHMITD[1], D. HAMBARDZUMYAN[5,6], R. J. GIGER[1,4];
[1]Cell and Developmental Biol., Univ. of Michigan, Ann Arbor, MI; [2]Cell and Developmental Biol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [3]Dept. of Chem., Univ. of Michigan, Ann Arbor, MI; [4]Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI; [5]Dept. of Oncological Sci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [6]Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, New York, NY

Abstract: Trauma to the mammalian peripheral nervous system (PNS) triggers a complex immune response that is crucial to recovery. However, it remains unclear how and to what extent different immune cell types contribute to or inhibit nerve repair. The early immune response to sciatic nerve crush (SNC) is dominated by polymorphonuclear neutrophils (PMN) and pro-inflammatory Ly6C^{hi} monocytes (Mo) followed closely by Ly6C^{lo} Mo. It is unclear if Ly6C^{lo} Mo differentiate from Ly6C^{hi} Mo or infiltrate the injured nerve sequentially. Studies in injured non-neural tissues suggest that Mo derived macrophages (MDM) originating from Ly6C^{hi} or Ly6C^{lo} Mo have distinct phagocytic activities. In the injured sciatic nerve, MDM contribute to the clearance of myelin debris and apoptotic cells. Previous studies have used chemokine receptor 2 mutant mice (*Ccr2-/-*) to investigate the role of Mo in PNS injury. However, redundancies in chemokine ligand/receptor pairs resulted in incomplete blockade, making results difficult to interpret. Recently, a new mouse called quintuple monocyte chemoattractant protein (*qMCP-/-*), was developed that is deficient for 5 chemokines (*Ccl2/7/8/11/12*) to block all Mo trafficking. Here, we sought to characterize the immune response to SNC in the absence of nerve infiltrating Mo, and study the impact on nerve debridement, axon regeneration, target innervation, and the development of chronic pain. To address these questions, we subjected adult WT, *Ccr2-/-* and *qMCP-/-* mice, split evenly by sex, to SNC. We then assessed immune cell profiles in naïve and injured nerves at 1, 3, and 7 days-post-crush (dpc) by flow cytometry. No sex-dependent differences were observed. At 1dpc, Ly6C^{hi} Mo are absent from injured nerves of both *Ccr2-/-* and *MCP-/-* mice but abundantly found in WT. At 3 dpc Ly6C^{lo} Mo are present in *Ccr2-/-* nerves, but not *qMCP-/-* mice suggesting *Ccr2* independent mechanisms for Ly6C^{lo} Mo accumulation in the injured nerve. By 7 dpc, macrophages (Mφ) begin to accumulate in the *qMCP-/-* nerve, likely representing the proliferation of tissue resident Mφ. PMN infiltrate the injured nerve at 1 dpc similarly between genotypes, however their clearance is delayed from mutant nerves. At 3 and 7 dpc, *Ccr2-/-* nerves contain more PMNs than WT nerves, and *qMCP-/-* nerves contain significantly more PNM than *Ccr2-/-* nerves. This indicates dependence on infiltrating MDMs for timely clearance of PMN. Ongoing studies are aimed at characterizing the PMN, Mo and Mφ that respond to SNC in *qMCP-/-* and investigating the relationship between these populations, nerve debridement, repair, and neuropathic pain.

Disclosures: H. Hafner: None. **X. Zhao:** None. **D. Wilborn:** None. **M. Athaiya:** None. **L. Schmitd:** None. **D. Hambardzumyan:** None. **R.J. Giger:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.12/C153

Topic: C.06. Neuromuscular Diseases

Support: K08 AR060164-01 A
W81XWH-16-1-0725

Title: Erythropoietin enhances Schwann cell repair and phagocytosis to accelerate nerve regeneration after sciatic nerve injury

Authors: P. GOVINDAPPA, G. ELLUR, R. VELIKKAKATH GOPI, A. GABER, *J. ELFAR; The Univ. of Arizona, Col. of Med., Tucson, AZ

Abstract: Traumatic peripheral nerve injury (TPNI) destroys axons and Schwann cells (SC), which must be cleared early by surviving SCs through phagocytosis before the recruitment of macrophages. To accelerate the process, SCs must be transformed into repair SCs following TPNI. Failure to transition inhibits phagocytosis, exacerbates inflammation/ apoptosis, and impairs SC re-differentiation (pro-myelin/myelin SC) for axonal regeneration and functional improvement. Our recent study showed that erythropoietin (EPO), a US-FDA-approved anti-anemic cytokine, guided nerve regeneration by promoting macrophage phagocytosis post-TPNI. However, the significance of its effects on SC phagocytosis and reparative transition is unclear. We hypothesized that EPO's neuroprotective function through SCs may be due to its role in supporting SC early repair and phagocytosis following TPNI. We used 10-week-old-male C57BL/6J mice weighing 25 ± 3 g to perform sciatic nerve crush injury (SNCI) using calibrated jig-modified forceps for 30 s. All animal experiments were approved by the IACUC committee of The University of Arizona College of Medicine, Tucson, AZ. Animals (n = 6 /group) were randomly assigned to sham (normal saline, 0.1 ml/mouse), SNCI (normal saline, 0.1 ml/mouse), and SNCI with EPO (5000 IU/kg) groups. Saline/EPO was given intraperitoneally immediately after surgery and post-surgery days 1 and 2. The sciatic functional index (SFI) following nerve injury was assessed on days 1, 3, 5, and 7. Mice were euthanized on post-injury days 3 and 7 to analyze SC phagocytosis, apoptosis, and repair-phenotype (myelin vs. non-myelin) using immunofluorescence (IF) staining. *In-vitro* phagocytosis of dead-SC and SC repair function under lipopolysaccharide (LPS)-induced stress conditions were analyzed using IF and Western blotting, respectively. Data were analyzed using either one-way ANOVA or unpaired t-tests. Our results showed that EPO significantly improved SC early repair (p75NTR vs. MPZ expression) and phagocytosis of myelin debris on days 3 and 7 following SNCI. *In-vitro* SC study also confirmed the significance of EPO treatment for accelerating efferocytosis of dead SC and re-differentiation of SC (MPZ, SOX10, EGR2 vs. c-JUN and p75NTR) under LPS conditions. EPO also showed an anti-apoptotic effect via mitigating SCs apoptosis on days 3 and 7 following SNCI. To the best of our knowledge, this is the first study to demonstrate EPO’s augmenting effect on SCs reparative and phagocytosis functions, which helps to improve re-myelination and SN functional recovery following SNCI.

Disclosures: P. Govindappa: None. **G. Ellur:** None. **R. Velikkakath Gopi:** None. **A. Gaber:** None. **J. Elfar:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.13/C154

Topic: C.06. Neuromuscular Diseases

Support: NINDS 1R01NS105725
NYS DoH C33267GG
NIGMS 1S10OD028547

Title: Neuroimmune Signaling Through Adenosine Supports Peripheral Nerve Regeneration

Authors: *N. LI[1], J. JARA[2], M. SOLIMAN[1], R. PATIL[1], A. BERNSTEIN[1], D. E. WILLIS[1], E. R. HOLLIS[1];
[1]Burke Neurolog. Inst., White Plains, NY; [2]Scripps Res. Inst., La Jolla, CA

Abstract: Title: Neuroimmune Signaling Through Adenosine Supports Peripheral Nerve Regeneration**Authors:** Na Li[1*], J. Sebastián Jara[1,2*], Marwa Soliman[1], Richa Patil[1], Amanda Bernstein[1], Dianna Willis[1,3], Edmund Hollis[1,3]1. Burke Neurological Institute, White Plains, NY2. Scripps Research Institute, La Jolla, CA3. Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY * These authors contributed equally to this work.**Abstract:**Peripheral nerve injury triggers a cascade of changes, including a calcium wave which propagates from the distal injury site to the cell soma, resulting in a transient increase in the second messenger cyclic adenosine monophosphate (cAMP) and the initiation of a robust pro-regenerative state in dorsal root ganglia (DRG) neurons. This conditioning effect can be mimicked using antidromic electrical or optogenetic activation of peripheral axons; however, effective axon regeneration also requires that intracellular calcium activity be attenuated. Within the central nervous system, microglia play a critical role in suppressing synaptic activity by producing adenosine through ATP catabolism. Adenosine then binds A1R receptors on synaptic partners, reducing neuronal activity.Within the DRG, peripheral macrophages express several components of ATP hydrolysis, and our data indicate that they play a similar role to that of microglia at central synapses, linking suppression of sensory neuron activity via adenosine purinergic signaling as a key step in supporting axon regeneration. DRG macrophages respond to nerve injury by enwrapping large-diameter, regenerating sensory neurons, and macrophage depletion attenuates peripheral regeneration. While cytokine signaling is known to regulate the macrophage response to injury, the signaling pathway that supports sensory neuron regeneration has not been previously identified. Single-cell sequencing datasets confirm that key ATP hydrolysis pathways are present in injured DRGs. Here, we used a mouse model of sciatic nerve crush to test the hypothesis that neuroimmune interactions promote peripheral axon regeneration through adenosine signaling. We observed elevated levels of adenosine and macrophage

expression of ATP ectonucleotidases in DRGs after nerve crush. Pharmacological antagonists of ATP hydrolysis and the adenosine-A_1R signaling pathway reduce axon regeneration. These findings suggest that adenosine-mediated purinergic signaling and the interaction of primary sensory neurons with macrophages play a crucial role in supporting the regenerative process in sensory neurons after peripheral nerve injury.

Disclosures: N. Li: None. **J. Jara:** None. **M. Soliman:** None. **R. Patil:** None. **A. Bernstein:** None. **D.E. Willis:** None. **E.R. Hollis:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.14/C155

Topic: C.11. Spinal Cord Injury and Plasticity

Title: The Effectiveness of Melatonin and Fibrin Clot in Acute Sciatic Nerve Injury in Rats

Authors: M. TINGIR[1], N. GERGERLIOGLU[2], C. KURAL[3], S. BASARAN[3], A. KURAL[4], A. BAYRAK[3], ***H. S. GERGERLIOGLU**[5];
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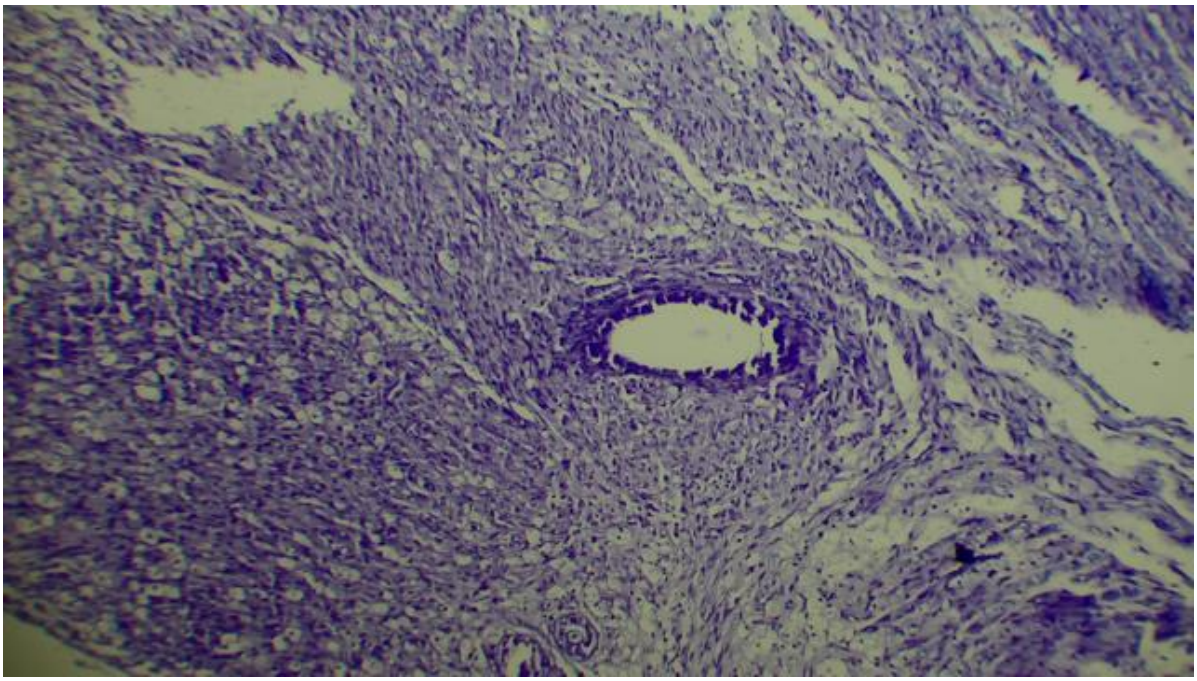
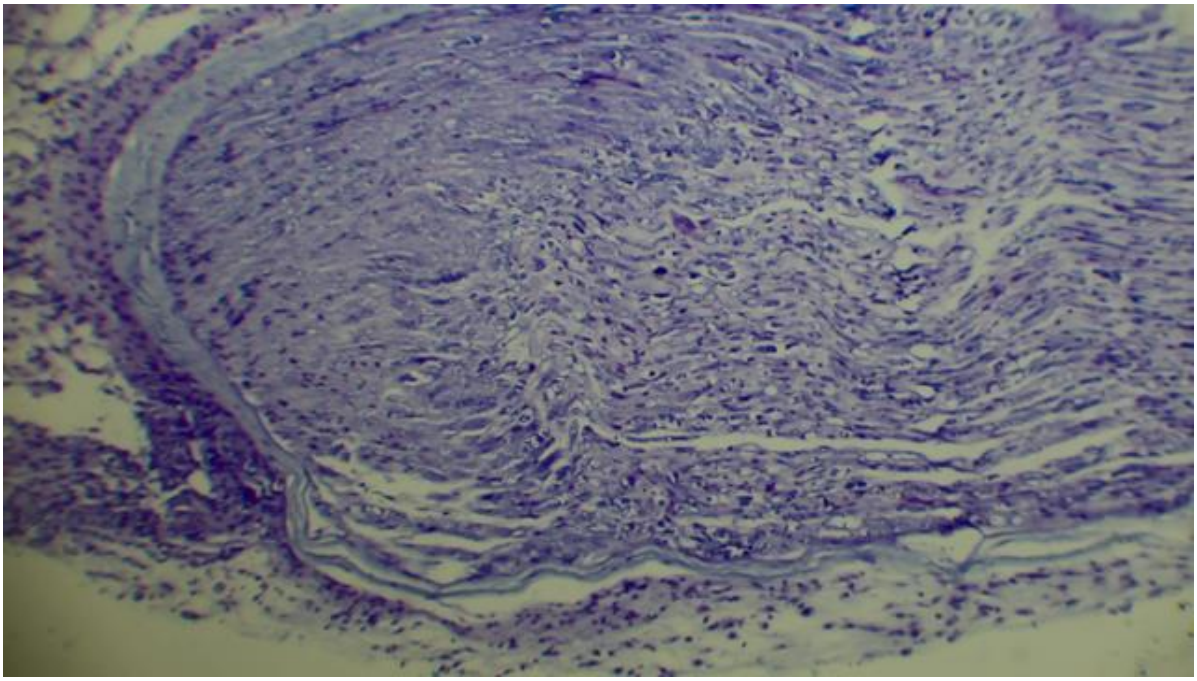
Abstract: The aim is to evaluate the effectiveness of melatonin and fibrin clot in acute sciatic nerve injury in rats. Twenty-seven Wistar-Albino adult rats were used, and incisions were made on the sciatic nerves. Group 1: The control group received primary repair. Group 2: The melatonin group received primary repair + weekly melatonin. Group 3: The melatonin + fibrin clot group received primary repair + fibrin clot + weekly melatonin. Blood samples were taken on days 1, 3, and 7 for Total Antioxidant Status analysis. After biomechanical evaluation, three rats from each group were sacrificed weekly and underwent histopathological examination. There was no statistically significant difference in absorbance and concentration measurements among the groups on the 3rd day. The changes in regeneration, inflammation, fibrosis, neovascularization, and vacuolization scores of the control group rats at 1st week, 2nd week, and 3rd week were ($p>0.05$). Changes in regeneration scores of the melatonin group at 1st week, 2nd week, and 3rd week were statistically significant ($p<0.01$). Melatonin usage is significant due to its high safety margins and low cost, and its use in acute sciatic nerve injuries seems promising.





Disclosures: M. Tingir: None. **N. Gergerlioglu:** None. **C. Kural:** None. **S. basaran:** None. **A. Kural:** None. **A. Bayrak:** None. **H.S. Gergerlioglu:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.15/C156

Topic: C.06. Neuromuscular Diseases

Support: NRF

Title: Reduced graphene oxide-based conductive hydrogel for peripheral nerve regeneration

Authors: *J. PARK[1], H. KONG[2];
[1]Univ. of Illinois Urbana-Champaign, Urbana, IL; [2]Chem. & Biomolecular Engin., Univ. of Illinois Urbana-Champaign Neurosci. Grad. Program, Urbana, IL

Abstract: Peripheral nerve injuries pose a significant challenge in medical treatment, often leading to long-term disability. Traditional surgical methods like nerve grafting have limitations, including donor site morbidity and scarce graft materials, necessitating innovative alternatives for effective nerve regeneration. Nerve guidance conduits (NGCs) offer a promising substitute for conventional nerve repair methods. These conduits act as physical guides that support and direct the growth of regenerating nerve fibers, potentially bridging nerve gaps without the need for direct suturing or grafts. The optimal NGC should actively promote regeneration through biochemical cues, topographical guidance, and electrical stimulation. Our research focuses on designing multifunctional NGCs using a combination of graphene oxide (GO) and gelatin-methacrylate (GelMA). The electrical conductivity and mechanical strength of graphene oxide, coupled with the biocompatibility of gelatin-methacrylate, make this mix particularly effective for nerve regeneration. By polymerizing and chemically reducing these materials, we created reduced graphene oxide/gelatin-methacrylate (r(GO/GelMA)) NGCs. These conduits exhibit essential properties such as flexibility, mechanical stability, permeability, and improved electrical conductivity. We evaluated the effectiveness of r(GO/GelMA) NGCs through comprehensive in vitro and in vivo studies. In vitro tests with PC12 neuronal cells showed that r(GO/GelMA) conduits enhanced neuritogenesis significantly more than GelMA and unreduced GO/GelMA. In vivo experiments using a rat sciatic nerve injury model with a 10 mm gap further confirmed the NGCs' efficacy in enhancing peripheral nerve regeneration. This was demonstrated by increased muscle mass, improved electro-conduction velocity, and enhanced sciatic nerve function index, supported by positive histological, immunohistological, and morphometrical results. This study highlights the potential of electrically conductive hydrogel NGCs as effective conduits for peripheral nerve repair, illustrating their capability to not only mimic nerve tissue structure but also actively promote nerve tissue healing and regrowth.

Disclosures: J. Park: None. **H. Kong:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.16/C157

Topic: C.06. Neuromuscular Diseases

Support: Belle Carnell Regenerative Neurorehabilitation Fund

Title: Impact of BDNF Val66Met Polymorphism on Therapeutic Electrical Stimulation Outcomes in Peripheral Nerve Regeneration

Authors: J. WALTERS[1], M. QUEZADA[2], S. HE[3,4], ***C. K. FRANZ**[1];
[1]Biologics, Shirley Ryan AbilityLab, Chicago, IL; [2]Northwestern Univ., Chicago, IL; [3]Biol., Univ. of Virgina, Charlottesville, VA; [4]Biomedical Engineering, Northwestern University, Evanston, IL

Abstract: The goal of this study was to investigate the impact of Brain-Derived Neurotrophic Factor (BDNF) Val66Met polymorphism on therapeutic electrical stimulation (TES) for peripheral nerve regeneration. We conducted a preclinical study in a rat model to explore interactions between an established TES paradigm supported by multiple clinical trials, and the Val66Met genotype, which is a genetic polymorphism carried by approximately 1/3rd of the US population that may impair the therapeutic mechanism of TES. Briefly, peripheral nerve injuries (PNIs) significantly challenge clinical medicine, affecting over 200,000 individuals annually in the United States. Despite some capacity for regeneration, most patients experience slow and incomplete recovery, often leading to permanent disability and severe neuropathic pain. TES is emerging as a promising intervention that promotes axon regrowth and improves muscle reinnervation, primarily through enhancing BDNF signaling via its TrkB receptor. However, variability in clinical outcomes is significant, influenced by factors such as age, sex, and medical comorbidities. The interplay between genetic variations and PNI outcomes remains largely unexplored. This study focuses on the Val66Met polymorphism in the BDNF gene, known to impair BDNF secretion in response to activity-based therapies like electrical stimulation. Understanding this gene-treatment interaction is crucial as BDNF plays a pivotal role in PNI and affects TES efficacy. To clarify terminology, the Val66Met polymorphism in humans corresponds to the Val68Met polymorphism in rats. Thus, our study utilized a Val68Met rat line with either the Met or wild-type (Val) alleles, who underwent transection and direct repair of the tibial nerve. Rats received either one hour of TES (20 Hz, 3V, continuous and biphasic) or a sham treatment. Outcome assessments included muscle cross-sectional area, muscle reinnervation, and fiber cross-sectional area. Additionally, we employed an isogenic human stem cell model to isolate the effects of the BDNF Val66Met polymorphism on activity-dependent BDNF release by motor neurons. Our results indicate that TES leads to greater muscle cross-sectional area, muscle reinnervation, and fiber cross-sectional area in Val allele carriers, but not in Met allele carriers. Furthermore, our in vitro model demonstrates that this common genetic polymorphism impairs activity-dependent BDNF release in Met allele carriers. These findings underscore the importance of considering genetic variations in therapeutic interventions for peripheral nerve regeneration as we advance toward an era of precision rehabilitation medicine.

Disclosures: J. Walters: None. **M. Quezada:** None. **S. He:** None. **C.K. Franz:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.17/C158

Topic: C.06. Neuromuscular Diseases

Support: PAPIIT UNAM (IN207524, IN215522, IN207624, IN209124)
CONAHCYT (214971)

Title: Analysis of the effect of GH and GnRH administration on the regeneraton of the injured rat sciatic nerve

Authors: *J. J. BACA ALONSO[1], I. HERNÁNDEZ-JASSO[1], D. CALDERÓN-VALLEJO[1], C. ARÁMBURO[2], J. L. QUINTANAR-STEPHANO[1], C. G. MARTÍNEZ-MORENO[2];
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[2]Neurobiología Celular y Mol., Inst. de Neurobiología, UNAM, Querétaro, Mexico

Abstract: AbstractPeripheral nerve injury currently has no treatment that directly addresses nerve repair. In the present study, a treatment consisting of two hormones that have already been previously used to restore neurological damage is proposed: gonadotropin-releasing hormone (GnRH) and growth hormone (GH). Each one has been evaluated separately against symptoms of neural injury and they are proposed to have a synergistic effect that can enhance the constitutive regeneration observed after sciatic nerve injury. For this study, male Wistar rats with 250-300 grams of weight underwent castration surgery and were subsequently injured by complete transection of the sciatic nerve. They were divided into 5 groups: SHAM, SS (saline solution), GH, GnRH, and GH+GnRH. To evaluate nervous recovery, motor tests such as the walkway, open field, and Rotarod were performed; and sensitive tests such as the thermal plate and Von Frey filaments, along with a histological analysis of the soleus muscle to measure muscle atrophy. qPCR and immunofluorescence techniques were used for recovery analysis. The result obtained indicates that the injury of the sciatic nerve has a direct detrimental effect on hindlimb function. In terms of motor function, the opening of the ankle angle, the sciatic functional index, the distance traveled in the open field, and the latency of movement within the Rotarod were evaluated. Both the GH and GnRH groups showed significant improvement compared to the damaged group. Regarding the recovery of sensory function, the latency time on the thermal plate and the 50% threshold in the Von Frey filaments were evaluated, with only the GnRH group presenting recovery of sensitivity. For the molecular analysis, the markers BDNF, GAP43, Iba-1, and TNFα were analyzed, with GH and GnRH treatments returning to normal expression values. MBP was measured in immunofluorescence, with the GH and GnRH groups presenting higher expression in comparison to injured rats. A favorable effect has been recorded for the treatment of GH and GnRH since the tests show effects on nervous recovery. These hormones have an individual neuroregenerative effect, which is lost when administered together, as the group of rats with the combined treatment did not show recovery.

Disclosures: J.J. Baca Alonso: None. **I. Hernández-Jasso:** None. **D. Calderón-Vallejo:** None. **C. Arámburo:** None. **J.L. Quintanar-Stephano:** None. **C.G. Martínez-Moreno:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.18/C159

Topic: C.06. Neuromuscular Diseases

Support: DoD Grant W81XWH-20-PRMRP-IIRA

Title: Development of Bionic Exoskeleton Control via the Muscle Cuff-Regenerative Peripheral Nerve Interface (MC-RPNI) in a Rat Model

Authors: *Y. TIAN[1], H. KUPERUS[2], K. BURKE[3], K. KOZMA[1], R. KODALI[3], W. ADIDHARMA[3], B. GILLESPIE[4], S. W. KEMP[3];
[1]Biomed. Engin., [2]Mechanical Engin., [3]Section of Plastic Surgery, [4]Robotics, UNIVERSITY OF MICHIGAN- ANN ARBOR, Ann Arbor, MI

Abstract: Foot drop is a common clinical problem that is characterized by difficulty in foot dorsiflexion, thereby increasing the risk of unstable gait and falling. Impairment of peroneal nerves is one of the major causes. As a potential solution to provide dorsiflexion movement based on an individual's intent, assistive exoskeletons have been developed. However, the state-of-the-art exoskeleton systems that interface with peripheral nerves to decode the user's intent and assist with corresponding movement are limited due to low signal amplitudes and poor signal-to-noise ratios. To improve the signal quality and create a stable bionic interface, we have developed the Muscle Cuff-Regenerative Peripheral Nerve Interface (MC-RPNI) where a free muscle graft was wrapped circumferentially around an intact nerve. The muscle cuff becomes a bio-amplifier (typically in millivolts) for the motor signals from the nerve (typically in microvolts) and therefore improves signal decoding and exoskeleton control. In this pilot study, the MC-RPNI was placed around the common peroneal (CP) nerve in the right hindlimb of an uninjured rat that underwent treadmill ambulation training and maintenance. We showed that the MC-RPNI construct remained viable with reinnervation and revascularization after a 3-month maturation period, and that distal muscle function was not impaired. In free-moving rats with implanted electrodes, we demonstrated that the MC-RPNI construct effectively amplified peripheral nerve signals in real time. To further evaluate the physiologic signaling of the MC-RPNI that correlates to volitional ambulation of the rat, we implemented six cameras (Optitrack) around the treadmill and securely placed motion capture markers on the hip, knee, ankle, and 5th metatarsal to capture the gait and motion of the rat. MC-RPNI signals were simultaneously recorded. Based on the motion tracking data, we calculated the ankle joint angles during multiple gait cycles. The MC-RPNI had increased signal amplitude during the dorsiflexion phase (i.e., Toe-off to Mid-swing), showing that the construct effectively amplified CP nerve signals physiologically. In conclusion, the MC-RPNI is a viable bionic exoskeleton interface and can transduce high-amplitude physiologic volitional motor signals for exoskeleton control.

Disclosures: Y. Tian: None. **H. Kuperus:** None. **K. Burke:** None. **K. Kozma:** None. **R. Kodali:** None. **W. Adidharma:** None. **B. Gillespie:** None. **S.W. Kemp:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.19/C160

Topic: C.06. Neuromuscular Diseases

Support: Edmonton Civic Employees Charitable Assistance Fund RES0063874
Canadian Institutes of Health Research RES 0042537

Title: Exploring the bone-nerve axis: exercise-induced secretion of osteocalcin from bone promotes nerve regeneration.

Authors: *K. N. RABEY[1], M. W. T. CURRAN[2], K. CHAN[3], J.-L. SENGER[5], C. A. WEBBER[4];
[1]Surgery, [2]Plastic Surgery, [3]Physical medicine and rehabilitation, [4]Div. of Anat., Univ. of Alberta, Edmonton, AB, Canada; [5]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Background and objectives: Peripheral nerve injuries are common and often disabling, with irreversible consequences. Regeneration of these nerves is challenging especially over long distances. Proximal nerve injuries have a poor prognosis and often result in permanent functional impairment and low bone mineral density (BMD) leaving the bone susceptible to fracture and osteoporosis. Exercise training has been used clinically to accelerate nerve regeneration, preserve muscle force, and promote BMD. During exercise, there is reciprocity of signaling molecules between bones, their corresponding muscles, and soft tissue to synchronize their function and growth. Osteocalcin (OCN) is released by osteoblasts during exercise to act locally (increasing bone strength) and systemically (improving insulin sensitivity and better diabetic control, both of which promote nerve health). The role of OCN after nerve injury has not been studied. Our lab has discovered that the OCN receptor, GPR158, is expressed in all subtypes of sensory neuronal cell bodies in the dorsal root ganglion (DRG) and motor neuronal cell bodies in the ventral spinal cord. We hypothesize that, in addition to increasing BMD, OCN is released from bone following exercise to promote nerve regeneration after injury. **Methods:** Osteocalcin knockout (*Ocn*$^{-/-}$) mice are deficient in two clustered genes (*Bglap1* and *Bglap2*) that encode the OCN protein. In this study, we compared the regenerative capacity of *Ocn*$^{-/-}$ and wild-type (WT) mice +/- voluntary-wheel running (EX), +/- sciatic nerve injury. **Results:** Regardless of genotype, EX groups increased BMD, compound muscle action potential (CMAPs), and muscle force compared to mice that did not exercise. ELISA confirmed elevated OCN in plasma from EX mice compared to non-exercised WT mice. We confirmed that *Ocn*$^{-/-}$ did not secrete OCN. DRG qRT-PCR analysis showed increased GPR158 expression in EX mice. Quantitative neurite extension analysis showed *Ocn*$^{-/-}$ DRG neurons had less innate outgrowth compared to WT controls. Exogenous OCN rescued DRG neurite extension in *Ocn*$^{-/-}$ mice, which have continued expression of GPR158 in their sensory neurons. The conditioning effect, in which pre-injury of the nerve promotes axon outgrowth, remains in *Ocn*$^{-/-}$ mice and exogenous OCN further promotes neurite extension. **Discussion:** In this study, we have identified a bone-nerve axis for nerve regeneration via the protein OCN. A better understanding of the pathways and the crosstalk between these skeletal and nervous systems will lead to novel insights towards

therapeutic targets to enhance nerve repair, improve BMD, and further exploit the power of exercise therapy.

Disclosures: K.N. Rabey: None. **M.W.T. Curran:** None. **K. Chan:** None. **J. Senger:** None. **C.A. Webber:** None.

Poster

PSTR336: Peripheral Nerve Trauma and Regeneration

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR336.20/D1

Topic: C.06. Neuromuscular Diseases

Support: Canadian Institute of Health Research Grant RES0042537
Canadian Graduate Scholarship - Master's

Title: Investigating the mechanism of conditioning electrical stimulation: identifying key parameters and signaling pathways

Authors: *P. B. HARDY[1], J.-L. SENGER[2], K. N. RABEY[3], K. CHAN[4], C. A. WEBBER[5]; [1]Surgery, Univ. of Alberta, Edmonton, AB, Canada; [2]Univ. of British Columbia, Vancouver, BC, Canada; [3]Univ. of Alberta, Edmonton, AB, Canada; [4]Univ. Alberta, Edmonton, AB, Canada; [5]Div. of Anat., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Background: Despite timely surgical intervention, regeneration following peripheral nerve injury remains insufficient for adequate functional recovery. Thus, new therapeutic interventions are necessary. Conditioning electrical stimulation (CES) has recently been shown to accelerate the innate rate of regeneration when administered 7 days prior to a nerve injury. Due to its non-injurious, non-inflammatory nature, CES proves to be a viable option for clinical translation to enhance recovery in chronic and acute nerve repair, and nerve transfer procedures. However, the parameters of CES have not yet been optimized. The minimum duration of stimulation, and the period between conditioning and injury (latency period) have not been investigated. Likewise, much of the mechanism of CES remains uninvestigated. However, cAMP and its downstream targets BDNF and pCREB are known to upregulate following CES. The cAMP downstream effectors PKA and EPAC have not been investigated in the context of CES. **Objectives:** We aim to establish the minimum duration of electrical stimulation and latency period required for CES, and identify key molecular pathways involved in the mechanism of CES. **Methods:** To investigate the minimum duration of CES, CES was administered for 60, 30, 10 or 0 minutes either 3 days prior to DRG harvest to assess regeneration associated gene (RAG) expression, or 7 days prior to nerve repair surgery to assess regeneration. To investigate the latency period of CES, CES was administered 7, 5, 3, or 1 days prior to either neurite extension assays or RAG analysis, and compared to unstimulated DRG controls. To investigate the involvement of cAMP and its mediators in CES, CES is administered 3 days prior to DRG harvest and culture, EPAC and PKA pathways are pharmacologically

inhibited and neurite extension assessed. **Results:** Our data demonstrates that as the duration of stimulation increases, the capacity for regeneration following injury also increases. The most effective regeneration occurred with 1 hour of CES, though 30 minutes also significantly increased regeneration. Latency periods between 3 and 7 days increased neurite extension in vitro, coinciding with the upregulation of RAGs. Pharmacological inhibition of EPAC alone, and EPAC and PKA in combination resulted in the partial ablation of the pro-regenerative effects of CES in vitro, suggesting a compensatory role for both mediators, but a potentially larger role of EPAC in the mechanism of CES.

Disclosures: P.B. Hardy: None. **J. Senger:** None. **K.N. Rabey:** None. **K. Chan:** None. **C.A. Webber:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.01/D2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: PA Department of Health 4100094294
NIH R01 NS104194

Title: Effects of spinal virally-delivered brain derived neurotrophic factor (AAV-BDNF) on the excitability of lumbar Shox2 neurons after SCI.

Authors: *D. GARCIA-RAMIREZ, N. J. STACHOWSKI, L. YAO, K. J. DOUGHERTY; Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Spinal cord injuries (SCIs) disrupt the descending control of the spinal locomotor neurons producing paralysis. However, the neurons responsible for the generation of locomotor rhythm and pattern are located in thoracolumbar spinal cord segments, below most injuries, and can be targeted directly or indirectly via primary afferents to restore locomotor function. Previous work in various animal models of SCI have shown that increasing the expression of BDNF, through viral delivery to lumbar spinal cord segments, produces locomotor improvements, including stepping in mice with complete spinal thoracic transection. Changes in the sensory afferent gating to spinal neurons have been shown recently. However, the direct effect of virally injected BDNF on the sensory afferent pathways to and the excitability of the locomotor neurons after SCI has not been studied. Here, we aimed to determine if BDNF-induced locomotor improvements are related to changes in the excitability of a group of spinal locomotor neurons that express the transcription factor Shox2. We performed experiments on spinal slices from adult Shox2::Cre;R26-lsl-tdTomato mice 4 weeks after a complete spinal T8/9 transection with or without AAV-BDNF injected below the lesion during the SCI surgery. We performed whole-cell patch clamp recordings from visually identified Shox2 neurons and electrically stimulated dorsal roots to record sensory afferent inputs to Shox2 neurons. We found

altered excitability of Shox2 neurons from SCI mice that received viral BDNF. In comparison with Shox2 neurons from untreated SCI mice, Shox2 neurons from SCI mice that received BDNF had more hyperpolarized resting membrane potentials, but higher action potential firing frequencies measured at rest and during depolarizing current steps. BDNF effects on the excitability of Shox2 neurons do not represent a restoration of the pre-injury state since Shox2 neuron excitability is unaltered after chronic complete transection at T8/T9. Our results suggest that virally-delivered BDNF produces changes in the locomotor circuitry that are consistent with locomotor improvements.

Disclosures: D. Garcia-Ramirez: None. **N.J. Stachowski:** None. **L. Yao:** None. **K.J. Dougherty:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.02/D3

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01NS126228

Title: Pdk 2 and 4 as modulators of macrophage metabolism after spinal cord injury

Authors: *A. M. BAUR[1,2], F. STAPENHORST FRANCA[2], R. KUMARI[2,3], H. J. VEKARIA[2], P. G. SULLIVAN[2,4], J. C. GENSEL[2,3];
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Abstract: The innate immune response post spinal cord injury (SCI) has been shown to promote an inflammatory response that inhibits regeneration but can potentially increase endogenous repair. The pro-inflammatory response has been linked to M1-type macrophages while pro-reparative responses are linked to M2-type macrophages. One main difference between the two types is their metabolism. M1 macrophages require glycolysis, fatty acid synthesis, and pentose phosphate pathway activity to increase reactive oxygen species (ROS) activity. This provides the quick energy required for phagocytosis, but the response can cause secondary damage. Alternatively, pro-regenerative M2 macrophage metabolism uses oxidative phosphorylation (OXPHOS) and fatty acid oxidation. These pathways support the sustainability of M2 macrophages to generate growth factors and promote tissue repair. Pyruvate dehydrogenase (PDH) converts pyruvate (a product of glycolysis) into acetyl-COA to enter the tricarboxylic acid (TCA) cycle and promote OXPHOS: M2 metabolism. Under pro-inflammatory conditions, pyruvate dehydrogenase kinase (PDK) inhibits PDH causing pyruvate to be converted into lactate and promotes glycolysis: M1 metabolism. We hypothesize that PDK inhibition using dichloroacetate (DCA) will influence the metabolism of the macrophages and increase the proportion of M2 macrophages. To test the efficacy of our target, we analyzed two different

approaches: bone marrow-derived macrophages from PDK2/4 knockouts (genetic manipulation) and bone marrow-derived macrophages from wild type (WT) mice treated with DCA (pharmacological manipulation). We stimulated the macrophages to M1 (LPS and IFN-g), M2 (IL-4), or M0 (no stimulus). Using the seahorse analysis, we noted differences in oxygen consumption rate (OCR) of M1 and M2 macrophages in PDK 2/4 knock outs compared to WT. Treating the WT M1 macrophages with DCA showed an increase in OCR in comparison to WT M1 macrophages without treatment. The data demonstrates that PDK is a promising target to drive reparative macrophages post-SCI.

Disclosures: A.M. Baur: None. **F. Stapenhorst Franca:** None. **R. Kumari:** None. **H.J. Vekaria:** None. **P.G. Sullivan:** None. **J.C. Gensel:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.03/D4

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Role of Rho-associated coiled-coil containing protein kinase in the spinal cord injury induced neuropathic pain

Authors: *K. KISHIMA[1], T. TACHIBANA[2], H. YAMANAKA[3], M. TOI[4], M. OKUBO[5], Y. T. DAI[6], K. NOGUCHI[7];
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Abstract: Background context: Spinal cord injury (SCI) can lead to increased phosphorylation of p38 in spinal cord microglia. This is one of the main causes for the development of persistent pain. Recently, we reported our study on the activation of p38 mitogen-activated protein kinases (MAPK) in spinal microglia, which has been considered the key molecule for the onset and maintenance of neuropathic pain after peripheral nerve injury, using a rat model. We also reported that the RhoA/Rho-associated coiled-coil containing protein kinase (ROCK) pathway mediates p38 activation in spinal microglia in peripheral nerve injury. But the precise mechanisms of neuropathic pain induced by SCI are still unclear.**Purpose:** This study aimed to examine the activation of microglia and the p38 MAPK expression in the lumbar spinal cord after thoracic SCI in rats, and the correlation to the therapeutic effect of ROCK inhibitor ripasudil in rats with SCI.**Study design:** Male Sprague-Dawley rats underwent thoracic (T10) spinal cord contusion injury using an Infinite Horizon impactor device. SCI rats received ROCK inhibitor ripasudil (24 nmol/day or 240 nmol/day) from just before SCI to 3 days after SCI.**Methods:** The mechanical threshold in the rat's hind paws was measured over four weeks.

Morphology of microglia and phosphorylation of p38 (p-p38) in the lumbar spinal cord and were analyzed using immunohistochemistry.**Results:** The p-p38 positive cell and Iba1 (a maker of microglia) positive area were significantly increased at the lumbar spinal dorsal horn (L4-5) 3 days and 7 days after SCI compared with the sham-control ($p<.05$), whereas phosphorylated p38 was co-localized with microglia. Three days after SCI, the intensity of phosphorylated p38 and Iba1 immunoreactive cells in the dorsal horn was significantly lower in the ripasudil treated groups than in the saline group. However, administration of ROCK inhibitor did not affect the numbers of microglia. Moreover, the withdrawal threshold of the ripasudil-treated rats was significantly higher than that of the saline-injected rats on 14 days and 28 days after SCI.**Conclusions:** Our results suggest that activation of ROCK in spinal cord microglia is likely to have an important role in the activation of p38 MAPK, which has been considered as a key molecule that switches on neuropathic pain after SCI. Inhibition of ROCK signaling may offer a means in developing a novel neuropathic pain treatment after SCI. It may help patients with neuropathic pain after SCI.**Clinical significance:** The findings in the present study regarding intracellular mechanisms suggest that modulation of ROCK signaling may be a focus for novel treatment for neuropathic pain after SCI.

Disclosures: K. Kishima: None. **T. Tachibana:** None. **H. Yamanaka:** None. **M. Toi:** None. **M. Okubo:** None. **Y.T. Dai:** None. **K. Noguchi:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.04/D5

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Daniel and Ada Rice Foundation

Title: Chronic Dynamics of the Spinal Cord Neuroimmune Response Following Contusive Injury in Mice

Authors: *N. WROBEL, D. KIM, R. G. FESSLER, B. T. DAVID;
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Abstract: In traumatic spinal cord injury (SCI), a primary mechanical insult to the spinal cord causes immediate tissue damage and neurological dysfunction. The primary injury is followed by a protracted series of events, termed “secondary injury”, which takes place over weeks or months and results in additional tissue damage. Primary injury also rapidly sparks a robust neuroimmune response within the spinal cord, consisting of activation of central nervous system (CNS) resident immune cells and infiltration by peripheral immune cells. The spinal cord neuroimmune response persists chronically and is regarded as a major influencer of the progression and severity of secondary injury. The present study characterizes the dynamics of the post-injury neuroimmune response throughout the first 6 months after contusive SCI in adult (10-12 week-

old) female wild type (C57BL/6) mice, receiving a moderate (50 kdyn) spinal cord contusion at T9. For each cohort, one group of mice received a T9 laminectomy and spinal cord contusion (n=8/time point), while the control group remained naïve (n=6/time point). Nine terminal assessment time points were included, ranging from 1 day to 6 months post-injury (each timepoint was replicated between 1 and 4 times). At each terminal time point, relative levels of helper T cells, cytotoxic T cells, regulatory T cells, as well as macrophages and microglia, were assessed via flow cytometry. Immunohistochemistry conducted on separate cohorts provided an additional measure of immune cell infiltration. Measures of locomotor (open-field task) and sensory (tail flick) function were used to identify correlations between behavioral recovery and the prevalence of certain immune cell types. The spinal cord neuroimmune response in mice exhibits a biphasic pattern, with one peak of peripheral immune cell infiltration within the first 2 weeks post-injury, then a second peak at 2 months post-injury. Both T cells and peripheral macrophages remain elevated at 6 months post-injury. At 6 months post-injury, higher immune cell infiltration correlates with more normalized sensory function but may also be associated with spleen hypertrophy. Our results highlight the persistent and highly dynamic nature of the SCI neuroimmune response and indicate that certain effects of the spinal cord immune environment on behavioral function and on the peripheral immune system are still developing even in the chronic phase of the injury.

Disclosures: N. Wrobel: None. **D. Kim:** None. **R.G. Fessler:** None. **B.T. David:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.05/D6

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01NS110385
NIH Grant R01NS079702
Yant Family Spinal Cord Regeneration Fund

Title: Neuronal EphB2 signaling drives persistent neuropathic pain following spinal cord injury

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Abstract: A significant portion of individuals impacted by spinal cord injury (SCI) experience chronic neuropathic pain (NP). A major mechanism underlying NP after SCI is hyperexcitability of pain-encoding neurons in spinal cord dorsal horn (DH). Activation of certain erythropoietin-producing hepatocellular carcinoma (Eph) receptor tyrosine kinases has been shown to increase

neuronal excitability through effects such as altered glutamatergic neurotransmission. We therefore investigated the potential role played by EphBs - in particular EphB2 - in SCI-induced NP. We employed a mouse of cervical level 5/6 (C5/6) hemicontusion SCI that results in persistent at-level mechanical allodynia, thermal hyperalgesia and spontaneous pain as measured by the Von Frey filament, Hargreaves, and mouse grimace scale assays, respectively. We first took an unbiased proteomics-based approach to analyze changes in expression and phosphorylation status of a large number of proteins after cervical SCI using an antibody microarray assay. Following SCI, EphB expression and signaling were significantly upregulated in intact C7/8 DH. Using a chemogenetic mouse model, we then found that inducible inhibition selectively of EphB1, EphB2 and EphB3 after SCI led to a robust reversal of already-established mechanical allodynia. Via in situ hybridization analysis in superficial laminae of C7/8 DH, we found that SCI induced a selective increase in expression of EphB2 (but not of EphB1 or EphB3) in both neurons and astrocytes. Based on these findings, we tested a novel, conditional EphB2 knockout mouse to investigate effects of EphB2-specific loss in the DH after SCI. We performed anatomically-targeted microinjection into C7/8 DH of an adeno-associated virus encoding Cre recombinase under either a human synapsin promoter to target neurons or a glial fibrillary acid protein promoter to target astrocytes. Excitingly, neuron-specific EphB2 knockout in the DH after SCI led to a significant reversal of mechanical allodynia, while astrocyte-specific EphB2 knockout did not impact post-SCI NP-like behavior. Collectively, these findings suggest that enhanced EphB2 expression and signaling underlie alterations in DH neurons that drive circuit hyperexcitability and consequent chronic NP following SCI.

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Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.06/D7

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NS097880 (MRD)
Commonwealth of Pennsylvania Department of Health #6826 (MRD)
T32 NS121768

Title: Increasing intraganglionic macrophage presence reduces sensory-discriminative but not affective components of pain after spinal cord injury in mice

Authors: *G. A. GIDDINGS[1], J. H. RICHARDS[2], A. ROGUER VITERI[3], J. DOWTIN-DORSEY[3], A. SRIDHARAN[3], M. R. DETLOFF[4];
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Philadelphia, PA; [3]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [4]Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Symptomology related to neuropathic pain consists of sensory discriminative and affective dysfunction. 60% of individuals with a spinal cord injury (SCI) experience these symptoms. Previous work has shown that bone marrow derived (BMD) macrophages infiltrate into the spinal cord at and below the lesion and are associated with pain pathophysiology. Furthermore, we showed that peripheral ablation of these BMD macrophages increases the incidence of SCI pain in rats. The current study explores the hypothesis that dorsal root ganglia (DRG) injection of the monocyte chemoattractant CCL2 will reduce incidences of pain and alter supraspinal expressions of depressive behavior after SCI.To study the effects of modulating peripheral macrophages post SCI, LysM-eGFP C57bl6 mice underwent a C5 unilateral SCI or laminectomy followed by a C7-8 intraganglionic injection of CCL2 or vehicle with Naïve mice as controls. Sensory discriminative pain-like behaviors were assessed using von Frey, Hargreaves, and mechanical conflict avoidance paradigm. Affective dysfunction was assessed using open field, forced swim and sucrose preference. 7-weeks after SCI, mice were perfused and tissue samples were taken from the lesion, C7-8 spinal cord and DRGs, S1 and ACC. Assessments of immune cell infiltration, sprouting, and resident immune cell activation were performed. CCL2 microinjection increased the number of eGFP+/CD68+ macrophages in the DRG regardless of SCI ($p<.05$). Unbiased hierarchal cluster analysis identified most SCI-CCL2 mice displayed significantly reduced mechanical allodynia ($p<.05$), but increased immobility time in forced swim ($p<.05$) and significantly reduced sucrose preference ($p<.05$). This indicates that while increasing DRG macrophages reduces the expression of sensory-discriminative pain-like behaviors, it may negatively impact mood and affective pain-like behaviors after SCI. Additionally, CCL2 treatment reduced eGFP+/CD68+ macrophages in the C7-8 dorsal horn in SCI mice from this cluster compared to other SCI mice($p<.05$). Preliminary assessment revealed no evidence of BMD macrophage presence in S1 and ACC. Ongoing work is identifying other immune cells that may be responsible for the propagation and maintenance of cortical inflammation and depressive-like behaviors following SCI. Together, these findings suggest a complex relationship between the macrophage and neural function at different nodes in the pain pathway. Future experiments will examine cortical immune cell activation on neuronal activity.

Disclosures: G.A. Giddings: None. **J.H. Richards:** None. **A. Roguer Viteri:** None. **J. Dowtin-Dorsey:** None. **A. Sridharan:** None. **M.R. Detloff:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.07/D8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation Grant 1001637
NIH Grant NS111037-01

Title: Effects of Nanotherapeutic Rolipram-PgP in the Spinal Cord and Dorsal Root Ganglia Associated with Improved Functional Recovery after Spinal Cord Injury

Authors: *M. R. DETLOFF[1], G. A. GIDDINGS[2], Z. LIAO[4], M. A. SINGER[1], P. J. MCGINNIS[1], J. R. WALKER[3], J. J. WHEELER[1], J. S. LEE[4];
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Abstract: Neuropathic pain is the most common sensory disability that occurs after a spinal cord injury (SCI), with current therapies only benefiting about 20% of those injured. This obviates the need for more effective treatments. Chronic inflammation and myeloid cell activation is a consistent feature of both chronic pain and SCI. We showed that macrophage ablation or inhibition of their infiltration into the dorsal root ganglia (DRG) after SCI increased pain. Thus, manipulation of macrophages may alter nociceptor hyperexcitability to decrease the probability of pain development. One method to drive macrophages to a pro-reparative phenotype is to enhance their cyclic adenosine 3,5'-monophosphate (cAMP) activity. Indeed, both SCI and chronic pain reduce cAMP activity, and increasing cAMP activity via PDE4 inhibition reduces inflammation from SCI and improves recovery of motor function. Since cAMP is ubiquitously expressed, we will deliver rolipram (Rm), a PDE4 inhibitor via a nanoparticle cationic amphiphilic co-polymer poly (lactide-co-glycolide)-graft-polyethylenimine (PgP, US patent 10,232,050) with the long term goal of targeting macrophages and microglia, specifically. Here, adult male Sprague Dawley rats received a mid-thoracic contusive SCI (200 kdyn) followed immediately by intrathecal injection of saline or Rm-PgP over the lumbar spinal cord. Half of rats in the Rm-PgP rats received additional IT injections of Rm-PgP 2 and 4 days later. A T9-10 laminectomy group was included as a control. Locomotor and sensory function were assessed via the BBB locomotor rating scale and von Frey tests preoperatively and for 6 weeks post-op. Rm-PgP treatment improved locomotor function, regaining consistent plantar stepping and some coordination, while saline-treated rats occasionally stepped ($p<.05$). von Frey testing revealed that single or multiple treatments of Rm-PgP reduced paw hypersensitivity compared to saline controls ($p<.05$). Importantly, there were no differences between single or repeated Rm-PgP treatment. Spinal cord and lumbar DRG were collected at 1 and 6 weeks post op. Immunocytochemistry revealed that Rm-PgP treatment increased tissue sparing, reduced ED1+ and increased Arg1+ macrophages at the lesion epicenter compared to saline-treated rats, and analysis of DRG tissue is underway. Together, these data indicate that Rm-PgP treatment is neuroprotective and may modulate the activation state of macrophages. Ongoing experiments are assessing the therapeutic efficacy of Rm-PgP treatments in chronic SCI.

Disclosures: M.R. Detloff: 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.; Axonis Therapeutics. **G.A. Giddings:** None. **Z. Liao:** None. **M.A. Singer:** None. **P.J. McGinnis:** None. **J.R. Walker:** None. **J.J. Wheeler:** None. **J.S. Lee:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.08/D9

Topic: C.11. Spinal Cord Injury and Plasticity

Support: T32 NS121768
NS097880

Title: Intrathecal Injection of Polarized Macrophage sEVs Attenuate Allodynia and alter Nociceptor Sprouting in Spinal Cord Injured Rats

Authors: *J. WHEELER[1], X. LUO[1], Y. TIAN[2], C. MARBLE[1], A. GHADERI[1], S. K. AJIT[2], M. R. DETLOFF[3];
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Abstract: The objective of this study was to explore the analgesic potential of polarized macrophage (Mϕ) small extracellular vesicles (sEVs) in a rat model of spinal cord injury (SCI)-induced neuropathic pain. Neuropathic pain is a prevalent and etiologically complex condition among those with SCI, with allodynia and hyperalgesia serving as hallmarks of the disease. Dysregulation of the inflammatory response is a critical component of neuropathic pain pathogenesis, promoting sensitization along the pain pathway. sEVs are nanoparticles secreted across cell types and participate in a wide range of homeostatic and pathological processes. Previous work from our lab suggests that sEVs from polarized Mϕs attenuate allodynia in a rat SCI model of neuropathic pain. However, the mechanisms by which this analgesic effect is produced in unclear. We hypothesize that sEVs from polarized Mϕs attenuate neuropathic pain by modulating the immune response after SCI, inducing nociceptor plasticity. To explore our hypothesis, we performed von Frey assessment of mechanical allodynia in female Sprague Dawley rats before and after a C5 unilateral contusion SCI, noting decreases in paw withdrawal threshold as an indicator of neuropathic pain. 14 days post injury (dpi), SCI rats received 10ug of sEVs derived from either LPS-stimulated or unstimulated RAW 264.7 Mϕs, or vehicle via lumbar puncture. von Frey data was analyzed using a mixed effects approach to determine the effect of each treatment on pain over time. At 18 or 35 dpi, cervical spinal cord and DRGs were dissected for immunohistochemistry of microglial/Mϕ activation (ED1, Iba1) and the distribution of nociceptive primary afferents (CGRP, IB4) in the dorsal horn. We are currently exploring the effects of sEV administration on nociceptor excitability after SCI from a subset of rats 4 days after sEV treatment via whole cell patch clamp of isolated IB4+ nociceptors. Our data shows that paw withdrawal thresholds to tactile stimuli decrease following SCI, and administration of sEVs from LPS-stimulated Mϕs restored withdrawal threshold to pre-injury levels for nearly two weeks post-injection. This effect was associated with decreased topographical distribution of nociceptive primary afferents in the dorsal horn. Immunohistological analysis of IBA1 expression indicated no change in microglial/Mϕ activation in the ipsilesional dorsal horn in response to treatment type. Analysis of membrane properties of nociceptors in each treatment group is underway. Our data suggests that sEVs from LPS-stimulated Mϕs could promote sustained analgesia in SCI rats by modulating the nociceptor.

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Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.09/D10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS R01NS102850
NINDS R21NS116665

Title: Dysregulated AD-LTMR signaling and peripheral TrkB plasticity contribute to chronic aversive pain after Spinal Cord Injury

Authors: S. PARVIN, *S. GARRAWAY;
Cell Biol., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: We recently showed that activation of C-Low threshold mechanoreceptors (C-LTMRs) signals aversive pain after spinal cord injury (SCI), accompanied by an acute elevation in respiratory rates (RRs) [Noble DJ et al, Front Int Neurosci 2022]. Here, we examine whether Aδ-LTMRs similarly contribute to pain after SCI. Aδ-LTMRs are small diameter cutaneous afferents that innervate hairy skin and signal directional touch. They express TrkB and require BDNF-TrkB signaling for normal function. The genetic identification of Aδ-LTMRs allows targeted investigation into their role, as well as BDNF-TrkB signaling, in pain after SCI. Adult $TrkB^{CreER}$ mice, which enable selective targeting of Aδ-LTMRs [via crosses with Ai9 (tdtomato) or Ai32 (channelrhodopsin-2) mice], received a contusion SCI at T10 or a sham surgery. At 1 and 3 weeks post-surgery (wks), mice were assessed for mechanical sensitivity with von Frey hairs. A modified light-dark chamber conditioned place aversion (CPA) paradigm was used to assess at-level (aversive) pain at 4 or 7 wks. The mice received 3 x 30 minutes bouts of brush or optical stimulation of the trunk and were evaluated for chamber preferences before and after stimulation. At 1, 3 or 7 wks, mice were sacrificed, and cellular assays undertaken to measure BDNF, TrkB and pERK expression in the injured spinal cord and adjacent trunk skin. SCI mice showed significant hind-paw hypersensitivity compared to pre-surgery baselines and sham controls ($p<.01$ to .0001; RM 2-way ANOVA). Optical stimulation of the trunk to selectively engage Aδ-LTMRs failed to induce an aversive pain response at 4 wks, although a significant conditioned response emerged at 7 wks ($p<.05$). Meanwhile, brush stimulation at 4 wks produced a conditioned response in SCI mice compared to shams ($p<.05$) and increased their RRs during stimulation ($p<.05$ to .01). Cellular assessments at 1 and 3 wks revealed that in general, BDNF and TrkB levels were reduced or unchanged in the lesioned spinal cord but elevated in the adjacent trunk skin ($p<.05$ to .001; t tests). Even at 7 wks, TrkB was decreased in the spinal cord ($p<.05$; t test), while its levels remained modestly upregulated in the skin ($p=.08$). pERK levels were also increased in the trunk skin of SCI mice at 3 wks ($p<.05$; t test).

Overall, these results reveal that whereas Aδ-LTMR activation does not appear to drive pain hypersensitivity at sub-chronic timepoints after SCI, it may contribute to aversive pain states during chronic SCI. Furthermore, the presence of peripheral TrkB plasticity suggests that dysregulation of Aδ-LTMRs is likely to contribute to neuropathic pain or other pathophysiology after SCI, although further investigation is needed.

Disclosures: S. Parvin: None. **S. Garraway:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.10/D11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS R01NS102850
NINDS R21NS116665

Title: Increased excitability in TrkB-expressing primary sensory neurons following spinal cord injury

Authors: *K. JANG, S. M. GARRAWAY;
Cell Biol., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Brain-derived neurotrophic factor (BDNF) and its receptor TrkB have been shown to promote both protective and pronociceptive effects. However, their contribution to neuropathic pain after spinal cord injury (SCI) needs further evaluation. We previously reported delayed onset of pain hypersensitivity after SCI in transgenic mice that enable systemic TrkB inhibition with 1NM-PP1 [*Martin et al., Front Cell Neurosci 2022*]. In a subsequent electrophysiological study of small-diameter dorsal root ganglia (DRG) neurons, we found that TrkB agonist (7, 8-dihydroxyflavone; DHF)-induced inward currents were decreased after SCI, suggesting that TrkB signaling in DRG neurons is likely not mediating pain hypersensitivity or nociceptor hyperexcitability. A potential caveat in the study is that cells were targeted by size (*i.e.*, small diameter), and their responsiveness to capsaicin, hence presumed to be nociceptors.
In this study we used $TrkB^{CreER}$ mouse crossed with Cre-dependent channelrhodopsin-2/EYFP (ChR2) mouse (TrkB::ChR2) and treated with tamoxifen (2 mg/day for 3 days; subcutaneous) to visually and selectively identify TrkB-expressing neurons. A cohort of mice received a contusion SCI at the thoracic (T) 10 level. T4-T12 DRGs were collected for dissociation from both uninjured and SCI mice at acute (5-7 days) and chronic (21-28 days) time points after injury. Whole-cell patch clamp recordings were made from the cultured neurons, and DHF (100 nM) was introduced. Furthermore, because TrkB works in conjunction with other receptors on DRG neurons, we also investigated involvement of voltage-gated sodium channels (Na_v) 1.7 and 1.8 by bath applying their respective inhibitors, tetrodotoxin (TTX) or A-803467 (A-803) to recorded neurons in the presence of DHF.

In uninjured mice, DHF induced an inward current that was significantly increased in SCI mice ($p=0.0083$; t-test) at both acute and chronic time points. Analysis of electrophysiological properties revealed a more negative resting membrane potential, and decreased capacitance, action potential half-width, and afterhyperpolarization duration, all suggesting increased neuronal excitability after SCI. Interestingly, inhibition of Na_vs 1.7 and 1.8 increased the inward current responses significantly ($p<.0001$; ANOVA), but only in the uninjured animals. Although the direction of change in response was surprising, that it was not replicated in the SCI group demonstrates that the SCI induced changes in Na_vs and their interaction with TrkB. Nonetheless, these results show that TrkB mediates increased excitability in DRG neurons that likely underlie the development of neuropathic pain after SCI.

Disclosures: K. Jang: None. **S.M. Garraway:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.11/D12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH/NINDS NS093055
UCSD VA RX002483
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T32 GM008666
Craig H. Nielsen Foundation
Wings For Life

Title: Understanding LZK-mediated reactive astrogliosis and neuronal repair using mouse molecular genetics and transcriptomic profiling

Authors: *K. AGBA[1], T. M. GAVIN[2], J. WU[3], M. CHEN[4], B. ZHENG[5];
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Abstract: After spinal cord injury (SCI), astrocytes become reactive in a process called astrogliosis. These reactive astrocytes surround the lesion and form an astrocyte scar border. Our lab recently previously discovered that LZK (or MAP3K13) regulates reactive astrogliosis and scar formation after a dorsal spinal cord crush injury. The effect of LZK-mediated astrogliosis on neural repair and regeneration is still not clear. We aim to investigate this question utilizing genetically modified mice and RNA sequencing. We are testing the effect of astrocytic LZK overexpression or deletion on behavioral recovery after a contusion injury. We will also assess the effect of the same LZK manipulations on corticospinal tract (CST) axon regeneration that is

induced by Pten suppression or IGF1/OPN overexpression. To identify potential downstream effectors of LZK signaling, we are setting up the RiboTag approach to examine the transcriptomic profiles of LZK-manipulated astrocytes. The relationship between the LZK and STAT3 pathways are also being examined with genetic analyses. Studying LZK-mediated astrogliosis provides an opportunity to dive deep into the mechanisms involved in astrocyte border formation and function. Together, these experiments will provide important insight into the cellular and molecular processes involved in astrogliosis and its functional consequences in SCI, which provides the basis for developing effective therapeutic interventions for spinal cord injury in the future.

Disclosures: K. Agba: None. **T.M. Gavin:** None. **J. Wu:** None. **M. Chen:** None. **B. Zheng:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.12/D13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIGMS T32 GM008666
NIH NS093055

Title: Characterizing the context-dependent role of DLK/LZK signaling in CNS injury response

Authors: *C. CHAVEZ-MARTINEZ[1,2], H. J. KIM[3], C. LONDONO[3], E. CHUANG[3], B. ZHENG[3];
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Abstract: Dual leucine zipper kinase (DLK) and leucine zipper bearing kinase (LZK) are closely related MAP3Ks that function in neuronal response to injury. DLK has been studied extensively, regulating both regeneration and apoptosis, among other outcomes. LZK has been shown to function redundantly with DLK. Our lab has previously shown that DLK and LZK together promote regeneration of corticospinal motor neurons (CSMNs) in a thoracic spinal cord injury model. We confirm that this is also the case following a cervical level spinal cord injury. Additionally, by axotomizing CSMNs subcortically in a distinct injury model, we show that DLK/LZK also promote CSMN death. As seen in retinal ganglion cells (RGCs), double deletion of DLK and LZK is more neuroprotective than single DLK or LZK deletion. We also find that this neuroprotective effect is temporary, as pyknosis proceeds in both wild-type and DLK/LZK-deleted neurons between 7- and 14-days post injury. We investigate how DLK and LZK promote both regeneration and death within cervical-projecting CSMNs using RiboTag-based RNA-sequencing.

Disclosures: C. Chavez-Martinez: None. **H.J. Kim:** None. **C. Londono:** None. **E. Chuang:** None. **B. Zheng:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.13/D14

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Applying spatial transcriptomics and mouse molecular genetics to understand the mechanisms of fibrotic scarring for promoting neural repair after spinal cord injury

Authors: *C. LONDONO[1], H. J. KIM[2], T. D. ARNOLD[4], R. DANEMAN[3], B. ZHENG[5]; [1]Neurosciences, Univ. Of California, San Diego, La Jolla, CA; [2]Neurosci., [3]UCSD, La Jolla, CA; [4]Pediatrics, UCSF - Pediatric Critical Care, San Francisco, CA; [5]Dept. of Neurosciences, Univ. of California San Diego, La Jolla, CA

Abstract: After spinal cord injury (SCI), fibroblasts become activated, proliferate, and migrate into the lesion site as a part of the wound-healing response termed fibrosis. Acutely, fibrosis restores tissue integrity and limits secondary damage, but chronically, known as the fibrotic scar, has negative effects on neural repair. Efforts to explore the mechanistic underpinnings of SCI fibrotic scarring are lacking. One candidate is transforming growth factor-β (TGF-β) signaling, which has been extensively characterized in fibrosis of the kidney, lung, and liver, while recently being implicated in central nervous system injuries. It is unknown whether TGF-β specifically regulates fibrotic scarring after SCI. We aim to determine the cellular mechanisms that regulate fibrotic scarring in the context of other cell types in the lesion microenvironment. First, we will validate the role of TGF-β signaling in fibrotic scarring by assessing the fibrotic scar of SCI mice with fibroblast-specific deletion of TGF-β receptor 2. Then, to assess how fibrotic scarring impacts the spinal cord injury site microenvironment, we will leverage spatial transcriptomics to obtain spatially resolved transcriptomic data of the injury site alongside reduced fibrotic scarring. We will also assess whether reducing fibrotic scarring increases corticospinal and serotonergic axon regeneration and improves functional recovery. Overall, this work will provide a better insight into the cellular and molecular processes involved in fibrotic scarring and elucidate its contribution to the injury site microenvironment after SCI, allowing for the general applicability of targeting fibrotic scarring for neural repair.

Disclosures: C. Londono: None. **H.J. Kim:** None. **T.D. Arnold:** None. **R. Daneman:** None. **B. Zheng:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.14/D15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Neilsen Foundation 648861
Neilsen Foundation 733544
NIH Grant NS093055

Title: Understanding spinal cord injury site dynamics with spatial transcriptomics

Authors: *H. KIM[1], C. K. AGBA[2], K. MONTE[2], C. LONDONO[2], A. CANFIELD[3], R. HUANG[3], J. ZHANG[3], E. HA[3], B. ZHENG[2];
[1]Neurosci., Univ. Of California San Diego Neurosciences Grad. Program, SAN DIEGO, CA; [2]Neurosci., UCSD, La Jolla, CA; [3]UCSD, La Jolla, CA

Abstract: Understanding the dynamics of the injury milieu after spinal cord injury (SCI) is key to developing effective therapeutic approaches. The injury site is complex and varies from injury to injury. First, various surgical methods are employed in animal research to model SCI. Some models are better suited to study axon regeneration such as the dorsal hemisection injury model, while others better mimic human SCI such as the contusion model. For spinal cord repair, a number of strategies have been developed to modify the injury environment such as manipulating astrogliosis through LZK gene overexpression and combining a scaffold and neural stem cell transplantation. Accordingly, multiple injury and repair models impact the injury site differently. To start to understand the spatially resolved gene expression changes in different SCI models, we have applied Visium spatial transcriptomics on various injury models including dorsal hemisection and contusion. By applying NNLS based deconvolution by leveraging existing snRNA-Seq data, we can detect dynamic cellular activities in the injury milieu. This approach allows for a detailed understanding of gene expression changes within diverse cell types at the injury site, offering valuable insights into the molecular mechanisms of SCI. In addition, we are extending this study to a repair strategy targeting LZK-mediated astrogliosis, which may lead ways to reduce the injury size and alleviate the inflammatory response.

Disclosures: H. Kim: None. **C.K. Agba:** None. **K. Monte:** None. **C. Londono:** None. **A. Canfield:** None. **R. Huang:** None. **J. Zhang:** None. **E. Ha:** None. **B. Zheng:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.15/D16

Topic: C.11. Spinal Cord Injury and Plasticity

Support: The Miami Project to Cure Paralysis
The Buoniconti Fund
NINDS R01NS081040

Title: Computational Evaluation of Cellular Pathology after SCI Using Single Cell and Spatial Transcriptomics

Authors: *C. FEHLBERG[1], J. CHOI[1], A. M. BRAKE[2], J. K. LEE[3];
[1]Univ. of Miami, Miami, FL; [2]NINDS, NIH, Bethesda, MD; [3]The Miami Project to Cure Paralysis, Univ. of Miami, Miami, FL

Abstract: We have integrated single cell and spatial transcriptomics technologies to elucidate the heterogeneity of cellular composition in the spinal cord before and after injury. As single cell sequencing lacks spatial information, and spatial sequencing lacks high cellular resolution, these two technologies complement each other to provide a more complete picture. Using single cell RNA sequencing of uninjured and 3 days post injury (dpi) mouse tissue we have found multiple subsets of activated microglia. In tandem with our single cell sequencing, we performed spatial transcriptomics four samples of 3 dpi tissue to elucidate the spatial heterogeneity of the early wound. We found that the linear progression of the microglial subpopulations over pseudotime corresponded to the localization of the cells in the spatial dataset after deconvolution. Spatial transcriptomics also resolved multiple regions in the early wound, which corresponded with distinct biological processes, without any a priori spatial or anatomical annotation. Gene ontology confirmed previously known discreet injury response mechanisms, and also revealed that antigen presentation may be an early driver of the formation of the astroglial border. These data provide new insights into the early resolution of injury at cellular and global scales.

Disclosures: C. Fehlberg: None. **J. Choi:** None. **A.M. Brake:** None. **J.K. Lee:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.16/D17

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Gene expression profile in spinal cord dorsal horn in spinal cord injury after intravenous infusion of mesenchymal stem cells

Authors: *R. FUKUSHI[1], M. SASAKI[2], O. HONMOU[1];
[1]Sapporo Med. Univ. Sch. of Med., Sapporo, Japan; [2]Neural Regenerative Med., Sapporo Med. Univ., Sapporo, Japan

Abstract: Introduction; Traditional spinal cord injury (SCI) research has focused on the recovery of motor function, but in recent years there has been increasing interest in the secondary effects associated with spinal cord injury. It is increasingly recognized that therapeutic

intervention for pain after SCI can significantly improve ADL and QOL. However, pain is intractable, and no effective treatment has been established. In actual clinical practice, we have seen many cases of SCI patients who have improved not only motor function but also spinal cord-induced pain after intravenous administration of autologous mesenchymal stem cells (MSCs). This study aimed to test whether MSCs administration can be an effective treatment for spinal cord injury pain. Furthermore, comprehensive gene expression analysis was performed to analyze the molecular mechanisms contributing to pain suppression. **Materials and Methods;** MSCs or vehicle were administered intravenously on day 3 after SCI model induction. The animals were maintained for 28 days with behavioral assessments over time. Ten rats in each of the MSC, vehicle, and sham groups were evaluated, and behavioral evaluations were conducted on days 3, 7, 14, 21, and 28 after model creation. The von Frey filament test, in which a mechanical stimulus is applied to the center of the hind paw plantar region using a filament, and the radiant heat test, in which a thermal stimulus is applied to the center of the hind paw plantar region and the escape reaction time is measured, were used as evaluation methods. Effects on the suppression of pain behavior were evaluated based on the presence or absence of allodynia and hyperalgesia. Next, total RNA was extracted from spinal dorsal horn tissue on day 28 for a comprehensive genetic analysis via microarray. **Results;** Number of escapes and times were measured via the von Frey filament test and radiant heat test, and results showed that pain behavior was suppressed in the MSC group compared with that in the vehicle group. Based on a comprehensive genetic analysis, 76 expression-altered genes were extracted with a fold-change less than or equal to −3 or greater than 3 and a p-value less than 0.05. Gene ontology and protein-protein interaction analyses of these differentially expressed genes revealed changes mainly associated with neurotransmitter- and channel related functions. **Conclusion;** MSC treatment based on a SCI model is suggested to alter gene expression in the spinal cord, contributing to pain amelioration. Integrated gene expression analysis revealed changes particularly in neurotransmitter- and channel-related gene clusters. It is expected that a detailed understanding of these profiles.

Disclosures: R. Fukushi: None. **M. Sasaki:** None. **O. Honmou:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.17/D18

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01 NS126228

Title: Assessing macrophage heterogeneity after spinal cord injury using open data

Authors: *F. STAPENHORST FRANCA, J. C. GENSEL;
Physiology; Spinal Cord and Brain Injury Res. Ctr., Univ. of Kentucky, Lexington, KY

Abstract: Following spinal cord injury (SCI), intraspinal inflammation takes place due to the destruction of microvasculature, leading to an influx of blood-derived inflammatory cells such as neutrophils and monocyte-derived macrophages. Macrophages, derived from microglia and monocytes, play different roles in wound healing, ranging from potentiating secondary injury to facilitating recovery and wound healing. *In vitro*, macrophages have been classified as proinflammatory M1 phenotype or regenerative M2 phenotype. *In vivo*, however, studies suggest that macrophages exist in a spectrum of phenotypes and can shift from one phenotype to another. Single-cell RNA sequencing (scRNA-seq) allows us to assess immune cell heterogeneity in the spinal cord after injury, and several groups have created datasets that are now publicly available containing valuable data to be explored further. In this study, we compiled different scRNA-seq datasets and analyzed macrophage heterogeneity after SCI based on cell clustering according to gene expression profiles. Using the Seurat pipeline, cells were clustered and macrophages were subsetted and reclustered in each dataset. Unique genes from each population were identified and the proportion of each cluster was assessed. Comparing across multiple datasets, the objective is to identify conserved macrophage populations that are consistently present after SCI independent of data source. The completion of this work will redefine macrophage heterogeneity in an unbiased and biological conserved approach.

Disclosures: F. Stapenhorst Franca: None. **J.C. Gensel:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.18/D19

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant

Title: Plexin-b1 mediates astrocyte mobilization to facilitate functional recovery after spinal cord injury

Authors: *H. NI[1], R. H. FRIEDEL[2], H. ZOU[3];
[1]Neurosci., Sch. OF Med. AT MOUNT SINAI, New York, NY; [2]Neurosci., Mount Sinai Sch. of Med., New York, NY; [3]Neurosci., Ichan Sch. of Med. at Mount Sinai, new york, NY

Abstract: Neural repair after spinal cord injury (SCI) involves the mobilization of astrocytes to form a protective glial barrier that seals the wound, limits inflammatory spread, and promotes wound compaction and matrix reorganization. This process involves coordinated physical movement and spatial organization of reactive astrocytes to confine immune cells at lesion core and form a rim of glial border separating the injury site from neighboring normal neural tissue. Here we show that reactive astrocytes upregulate axon guidance receptor Plexin-B1 in response to SCI. Plexin-B1 deletion impairs mobilization of astrocytes to form a protective glial border, leading to diffuse tissue damage, inflammatory spillover, and hampered axon regeneration. We

are currently conducting mechanistic studies to understand how Plexin-B1 deletion affects signaling communication between astrocytes and immune cells and other cell types at the injury site. Our data, therefore, establish Plexin-B1 as an important link that integrates biochemical cues and physical interactions of astrocytes with the injury microenvironment during wound healing.

Disclosures: H. Ni: None. **R.H. Friedel:** None. **H. Zou:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.19/D20

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01NS085426
NIH/NINDS Research Supplement to Promote Diversity in Health-Related Research

Title: Investigating the role of tubulin tyrosine ligase (TTL) in regrowth of adult sensory axons after chemogenetic neuronal activation

Authors: *A. ISLAM[1], V. J. TOM[2];
[1]Dept. of Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Injury to the mature nervous system most often results in permanent functional deficits. One factor limiting recovery is that neurons lose the intrinsic ability for robust axon growth after development. Our lab showed that activating adult dorsal root ganglia (DRG) neurons using chemogenetics, i.e., designer receptors exclusively activated by designer drugs (DREADDs), increases the ability to regenerate axons into the spinal cord after a dorsal root crush injury in vivo. *In vitro*, neurons were better able to grow past the inhibitory rim of CSPG spot assays. This increased growth may be attributed to microtubules, components of the cytoskeleton important for development, shape and motility, and organelle transport. Microtubules have two distinct domains, either stable or labile, depending on the type of post-translational modifications. While mature neurons contain a high concentration of stable (acetylated) microtubules in their axons, increasing stable microtubules may lead to forced polymerization of tubulin, causing abnormal axon growth. Meanwhile, labile (tyrosinated) microtubules are much more dynamic and are necessary for normal growth-cone motility and axon extension. We found that when adult DRG neurons are chemogenetically activated via the excitatory DREADD hM3Dq in vitro, there is an increase in labile, tyrosinated microtubules within the distal axon that mediates the improved axon outgrowth from activated neurons. We have found that axons in chemogenetically activated, $hM3Dq^+$ neurons have increased levels of tubulin-tyrosine ligase (TTL), a protein which tyrosinates tubulin, compared to growing axons

from neurons that do not express hM3Dq. We hypothesize that TTL plays a major role in the improved axon outgrowth observed after neuron activation via DREADDs. To directly test this hypothesis, we will examine axon growth from DREADD-activated neurons after shRNA-mediated knockdown of TTL. We will also investigate whether overexpressing TTL allows for control, non-chemogenetically activated neurons to exhibit comparable axon growth to DREADD-activated neurons. Elucidating the mechanisms involved in axon regeneration after neuron activation will identify potential molecular targets to increase the regenerative capability of adult neurons after injury.

Disclosures: A. Islam: None. **V.J. Tom:** None.

Poster

PSTR337: Spinal Cord Injury: Cellular and Molecular Mechanisms I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR337.20/D21

Topic: C.11. Spinal Cord Injury and Plasticity

Support: R21NS135769

Title: Overexpression of Sox11 restores embryonic, pro-growth gene transcription in adult cortical neuronal populations.

Authors: *E. C. BATSEL[1], M. G. BLACKMORE[2], Z. WANG[2], J. ROSAS[2], R. MOHAMMAD[3], D. O'SHEA[3];
[1]Marquette Univ. Dept. of Biol. Sci., Milwaukee, WI; [2]Biomed. Sci., Marquette Univ., Milwaukee, WI; [3]Marquette, Milwaukee, WI

Abstract: Mature axon pathways including the corticospinal tract (CST), fail to regenerate after spinal cord injury, leading to lasting dysfunction. In contrast, embryonic neurons display a high growth potential and rapidly extend axons toward their target cells. We have recently shown that adult CST neurons differ significantly in gene expression from their embryonic counterparts, with numerous genes showing at least a twofold up- or downregulation. Moreover, we find that adult CST neurons exhibit only a subdued transcriptional response to spinal injury, indicating that regeneration is limited in part by a failure to re-express regenerative transcripts. Thus, we aimed to identify a means to recapitulate an embryonic, pro-growth pattern of transcription in adult CST neurons. Here we focused on Sox11, a transcription factor that plays a role in promoting axon growth during development and which has been shown to enhance axon growth when overexpressed in adult neurons including CST. Our approach involved retrogradely labeling the cell nuclei of CST neurons through spinal injection of AAV2-retro-H2B-mGL and co-injecting AAV2-retro-Sox11 or control. After labeling, the animals were housed for two weeks followed by fluorescence-activated nuclei sorting and single nuclei sequencing (10X Chromium). Differential gene expression analysis was conducted in Seurat using Wilcoxon rank-sum tests, and ontological enrichment analysis was carried out using IPA. Sox11 produced large

changes in gene expression, with hundreds of genes significantly up or downregulated in cortical populations. In subcortical populations, Sox11 had a subdued effect. Ontological enrichment analysis revealed that genes upregulated by Sox11 were highly enriched for growth-relevant terms including axonogenesis and neuronal projection development and downregulated genes were linked to synaptogenesis. Importantly, these changes showed significant similarity to developmental gene changes. Sox11's striking transcriptional effects have motivated us to revisit its utility as an activator of axon growth. Current experiments are testing the transcriptional effect in injured cortical and subcortical neuronal populations to Sox11 overexpression in combination with potentially synergizing transcription factors. In addition, we are currently using a contusion model of spinal injury to test whether the transcriptional effects of Sox11 persist in the chronic injury state.

Disclosures: E.C. Batsel: None. **M.G. Blackmore:** None. **Z. Wang:** None. **J. Rosas:** None. **R. Mohammad:** None. **D. O'Shea:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.01/D22

Topic: C.11. Spinal Cord Injury and Plasticity

Support: W81XWH1910413

Title: The therapeutic efficacy of a novel treatment after spinal cord injury: Histological and functional investigation in a large animal model.

Authors: *S. JARLSDÓTTIR[1], J. WANG[1], A. PEI[1], R. CHAN[1], K. SO[1], N. MANOUCHEHRI[1], M. WEBSTER[1], J. ETHRIDGE[1], A. WARNER[1], A. BILLINGSLEY[1], A. DOELMAN[1], F. STREIJGER[1], C.-Y. LIN[2], Y.-S. LEE[2], B. K. KWON[3];
[1]ICORD, UBC, Vancouver, BC, Canada; [2]Cleveland Clin., Neurosci., Solon, OH; [3]Vancouver Spine Surgery Inst., Dept. of Orthopaedics, ICORD, UBC, Vancouver, BC, Canada

Abstract: Introduction: Animal models play a crucial role in medical research, serving as a valuable bridge between laboratory experiments and clinical trials. In particular, the Yucatan minipig is considered a useful translational model of spinal cord injury (SCI) given its larger size and anatomical similarities to humans. In this study, we aim to investigate the therapeutic potential of the CSPG Reduction Peptide (CRP) treatment in a porcine model of SCI. The CRP targets the injury scar tissue and distal perineuronal nets (PNNs), which are known to limit neuroplasticity after SCI. By examining the therapeutic efficacy of CRP treatment in this animal model, we hope to gain insights that could pave the way for new treatments for SCI patients. **Methods:** Following a T10 contusion/compression SCI, animals received either no treatment (n=7) or intrathecal CRP-infusion (n=11) for 12 weeks, starting 2 weeks post-SCI. After euthanasia at 14 weeks post-SCI, 20 spinal cords were collected and segments from thoracic,

lumbar and sacral levels were processed for histological analysis. Immunofluorescence (IF) staining was carried out, visualising alpha motor neurons (αMNs) with NeuN/ChAT-antibodies, CSPG-rich PNNs with Wisteria floribunda agglutinin (WFA), and serotonergic profiles with 5HT. Scar forming astrocytes were visualised using GFAP and CS-56 to examine changes in CSPG-expression. After imaging (20x), automatic image analysis was developed with intensity-based thresholds and machine-learning models, for IF-specific quantification (ZEISS Zen). **Results:** After SCI, histological investigation of the sacral porcine spinal cord revealed an upregulation of WFA-expression surrounding NeuN/ChAT positive αMNs. Furthermore, a significant reduction in the presence of 5HT positive varicosities was observed below the level of injury. In response to CRP-treatment, a further decrease in 5HT was observed in the spinal cord, specifically at the sacral level. There was no apparent influence on WFA-expression in PNNs throughout the cord following CRP-treatment, nor was there evidence of CSPG degradation within the injury scar. **Conclusion:** Initial findings revealed that the expression of serotonergic profiles following porcine SCI are comparable to previous findings in human spinal cords. This validates the application of the porcine model as a valuable translational model for further research. However, further investigations are necessary to assess the significance of subtle changes observed in response to CRP-treatment, which are presently ongoing, along with correlation analyses between histological and functional findings (locomotion and bladder function).

Disclosures: S. Jarlsdóttir: None. **J. Wang:** None. **A. Pei:** None. **R. Chan:** None. **K. So:** None. **N. Manouchehri:** None. **M. Webster:** None. **J. Ethridge:** None. **A. Warner:** None. **A. Billingsley:** None. **A. Doelman:** None. **F. Streijger:** None. **C. Lin:** None. **Y. Lee:** None. **B.K. Kwon:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.02/D23

Topic: C.11. Spinal Cord Injury and Plasticity

Support: US Department of Defense / Translational Research Award, Sponsor Reference Number: W81XWH2010480; SC190120

Title: Hemorrhage progression in a porcine model of SCI: the relationship to hemodynamic management and venous thromboembolism prophylaxis

Authors: *A. ALLARD BROWN[1], K. SO[1], N. MANOUCHEHRI[1], M. WEBSTER[1], J. ETHRIDGE[1], A. WARNER[1], A. BILLINGSLEY[1], R. NEWSOME[1], K. BALE[1,2], A. YUNG[1,2], C. GEE[1], J. WANG[1], M. SENEVIRATNE[1], J. CHENG[1], S. BASNAYAKE[1], F. STREIJGER[1], M. HERAN[3], P. KOZLOWSKI[1,2], B. K. KWON[1,4];
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of Radiology, Div. of Neuroradiology, Univ. of British Columbia, Vancouver, BC, Canada; [4]Vancouver Spine Surgery Institute, Dept. of Orthopaedics, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Introduction: After acute traumatic spinal cord injury (SCI), intraparenchymal hemorrhage (IPH) occurs due to the disruption of the spinal cord microvasculature. IPH presence on clinical magnetic resonance imaging (MRI) has been associated with a poor prognosis, making it crucial to understand how current treatment protocols for acute SCI patients influence IPH progression. In this pre-clinical study, we investigated the impact of mean arterial pressure (MAP) augmentation and venous thromboembolism (VTE) prophylaxis on IPH progression post-SCI. **Methods:** 30 female Yucatan pigs were randomly divided into five groups (N=6 per group) based on post-SCI treatments: 1) No treatment; 2) MAP augmentation over 7 days (starting 4 hours post-SCI); 3) Early VTE prophylaxis over 7 days (starting 12 hours post-SCI); 4) MAP augmentation + Early VTE prophylaxis; 5) MAP augmentation + Delayed VTE prophylaxis (starting 72 hours post-SCI). For MAP augmentation, Norepinephrine was used to increase MAP (20 mmHg above the daily baseline MAP) for 3 hours every day post-SCI for 7 days. For VTE prophylaxis, animals received a standard dose (1.5 mg/kg) of Enoxaparin via subcutaneous injection every 12 hours for 7 days. High-frequency *in vivo* ultrasound images of the spinal cord were captured before and hourly after injury until 7 hours to track early IPH progression. At the 7-day endpoint, the cord was collected for *ex vivo* 7-Tesla MRI and histological analysis. Spinal cord sections were stained to visualize blood and its breakdown products: Hematoxylin and Eosin (H&E) stained for red blood cells (RBCs) and Prussian blue stained for iron deposits, respectively. Robust semi-automated quantification pipelines were developed to measure IPH extent from ultrasound, MRI, and histology images. **Results:** During the initial 4-7 hours following SCI, IPH progression (Δ IPH volume and length) was not significantly exacerbated in the animals that received MAP augmentation (N=18) compared to those receiving no MAP augmentation (N=12). At 7 days post-SCI, no significant differences were observed between the five experimental groups in IPH volume or length on MRI. Histological analysis revealed no significant group differences in the RBC or iron extent (% cross-sectional area) +/- 16 mm around the injury epicenter. Furthermore, higher MAP values did not correlate with greater IPH progression over 7 days post-SCI. **Conclusion:** In our study, daily 3-hour MAP augmentation and VTE prophylaxis had no significant impact on IPH progression over 7 days post-SCI. Currently, we are in the process of analyzing IPH progression on ultrasound scans performed closer to the time of injury (< 4 hours post-SCI).

Disclosures: A. Allard Brown: None. **K. So:** None. **N. Manouchehri:** None. **M. Webster:** None. **J. Ethridge:** None. **A. Warner:** None. **A. Billingsley:** None. **R. Newsome:** None. **K. Bale:** None. **A. Yung:** None. **C. Gee:** None. **J. Wang:** None. **M. Seneviratne:** None. **J. Cheng:** None. **S. Basnayake:** None. **F. Streijger:** None. **M. Heran:** None. **P. Kozlowski:** None. **B.K. Kwon:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.03/D24

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Histopathology of posttraumatic syringomyelia in a porcine model of spinal cord injury

Authors: *R. CHAN[1,2], F. STREIJGER[1,2], J. WANG[1,2], S. JARLSDÓTTIR[1,2], J. MITCHELL[1,2], A. ZAIDI[1,2], B. K. KWON[1,2];
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Abstract: Posttraumatic syringomyelia (PTS) is a chronic condition that occurs in patients after spinal cord injury (SCI). It is characterized by the development of cerebrospinal fluid (CSF)-filled cysts, also known as syrinxes, in the spinal cord, months or years after the initial injury. Despite the prevalence of this condition, the underlying mechanisms leading to its development remain poorly understood. To shed light on the progression and histological features of PTS, this study utilizes the porcine model of SCI. T10 contusion-compression injury was induced in Yucatan miniature pigs by dropping a 50 g impactor onto the exposed spinal cord. Cords were harvested between 12 to 14 weeks later and stained with eriochrome cyanine for histological quantification. Cavitations were manually traced to calculate volume in histological sections. Additionally, *in-vivo* high-resolution ultrasound imaging was performed to visualize cavitations. Multilocular cavities were observed up to 46 mm from the epicenter of impact. These cavities were detected in several ultrasound scans and histological sections and were found to contain low-density tissue within the syrinx space. Cord regions caudal to the impact epicenter displayed relatively higher cavitation volume and length compared to rostral regions, with a cavity length of 4.9 ± 2.8 µm. Porcine cavitations exhibit a volume and distribution that can be compared to that of human PTS. The aforementioned similarities may have significant implications in providing valuable insights into the mechanisms underlying the syrinx formation and in providing a platform for the preclinical testing of potential therapeutic interventions.

Disclosures: R. Chan: None. **F. Streijger:** None. **J. Wang:** None. **S. Jarlsdóttir:** None. **J. Mitchell:** None. **A. Zaidi:** None. **B.K. Kwon:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.04/D25

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DARPA Award N66001-20-2-4046

Title: Establishing an index of spinal cord tissue oxygenation using near-infrared spectroscopy

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GRASSE[4], V. SIVAJI[4], R. SAINI[4], F. STREIJGER[1], B. K. KWON[1,5];
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Abstract: Introduction: We have developed a novel, implantable near-infrared spectroscopy sensor (D-NIRS) with the aim of continuously monitoring spinal cord tissue oxygenation following injury. This will allow for effective hemodynamic management of patients with spinal cord injury (SCI). One of the challenges in calculating absolute measures of spinal cord oxygenation, such as the Tissue Oxygenation Index (TOI), is the segmental blood supply of the spinal cord, which makes it difficult to calibrate TOI against blood gas measurements using standard clinical methods. To address this, we have adopted a two-step approach: 1) calibration to a reference NIRS device in a benchtop model of ischemia to ensure its accuracy and reliability; 2) conducting reproducibility testing in a porcine model, to verify that our device is effective in the *in-vivo* setting. **Methods:** During benchtop calibration, one D-NIRS sensor was placed on the thenar eminence and a series of 3-minute long limb ischemias were induced via surgical tourniquet. In total, 96 ischemias were collected across 3 individuals. The D-NIRS TOI was calibrated against a similar dataset that was previously collected using a reference NIRS device. In the *in-vivo* setting, two D-NIRS sensors were placed on the rostral and caudal segments of the intact thoracic spinal cord of n=6 Yucatan minipigs, and a series of 2 to 6 hypoxias were performed (sPO_2 target of 80%). Baseline TOI and % change in TOI per minute hypoxia (e.g. hypoxia sensitivity) were compared between the two D-NIRS sensors. **Results:** Within the benchtop calibration, a mean baseline TOI of 70.8% and 72.6% was found using the novel and reference NIRS device and an ischemia sensitivity of 8.8%/minute and 10.7 %/minute. In the *in-vivo* setting, baseline spinal cord TOI was (81.4 ± 5.2%) and the sensitivity to hypoxia was (2.58 ± 0.86 %/minute). The rostral and caudal D-NIRS sensors differed in baseline TOI and hypoxia sensitivity by an average of 1.97% and 1.02%/minute. **Conclusion:** The results demonstrate the reliability and effectiveness of our device, paving the way for further research. Ongoing research is being conducted to determine the clinical utility of spinal cord NIRS as well as to evaluate the relationship between NIRS TOI and other hemodynamic parameters, such as mean arterial pressure.

Disclosures: G. Frank: None. **K. Raschdorf:** None. **P. Alicea:** None. **A. Zaidi:** None. **N. Manouchehri:** None. **J. Ethridge:** None. **K. So:** None. **C. Levinsky:** None. **J. Mitchell:** None. **A. Billingsley:** None. **D.W. Grasse:** None. **V. Sivaji:** None. **R. Saini:** None. **F. Streijger:** None. **B.K. Kwon:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.05/D26

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Comparative Analysis of Invasive PO2 and Blood Flow Monitoring Systems in the Spinal Cord and Brain: Insights from a Porcine Model

Authors: *K. RASCHDORF[1], K. SO[2], J. ETHRIDGE[1], N. MANOUCHEHRI[3], A. ZAIDI[1], P. ALICEA[1], S. HAIDA[4], C. LEVINSKY[1], J. MITCHELL[1], G. FRANK[1], F. STREIJGER[1], B. K. KWON[5];
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Abstract: Introduction: Invasive intraparenchymal monitoring of tissue partial pressure of oxygen (PO2) and blood flow (BF) is well-established in cerebral contexts such as traumatic brain injury (TBI) and post-resuscitation care. Yet, its application in spinal cord injury (SCI) remains underexplored due to technical and procedural challenges. This study addresses two critical gaps: it aims to assess how spinal cord BF and oxygenation responses compare to those in the brain and evaluates the performance and agreement of various commercially available PO2 and BF sensors for spinal cord monitoring. By doing so, we aim to refine the methodologies used for spinal cord monitoring, contributing to the advancement of knowledge and understanding in the field of spinal cord research. **Methods:** We conducted four non-survival studies on uninjured female Yucatan miniature pigs, using different invasive BF and oxygenation sensors. The study monitored the spinal cord and brain simultaneously under conditions of hypoxemia (PaO2 < 80mmHg), hyperoxemia (PaO2 > 200 mmHg), hypocapnia (PaCO2 < 25 mmHg), and pharmacologically induced mean arterial pressure (MAP) changes (>10 mmHg). Tissue PO2 was monitored using Licox probes (Integra LifeSciences) and fluorescent quenching sensors (OxyLite, Oxford Optronics), while BF was assessed with Hemedex thermal diffusion probes and laser doppler flowmetry sensors (OxyFlow, Oxford Optronics). These were placed in the brain's subcortical white matter and at thoracic (T2) and lumbar (L1) spinal levels. **Results/Conclusions:** The study successfully monitored oxygenation and hemodynamics in the brain and spinal cord. Under hypoxemia, both regions showed decreased tissue PO2, whereas hyperoxemia induced an increase. Responses to hypocapnia triggered a reduction in BF, while MAP augmentations resulted in an increase in BF across both CNS compartments. This pilot study establishes the feasibility of simultaneous brain-spinal cord monitoring and underscores the analogous physiological responses between these CNS compartments, providing valuable insights for future clinical interventions.

Disclosures: K. Raschdorf: None. **K. So:** None. **J. Ethridge:** None. **N. Manouchehri:** None. **A. Zaidi:** None. **P. Alicea:** None. **S. Haida:** None. **C. Levinsky:** None. **J. Mitchell:** None. **G. Frank:** None. **F. Streijger:** None. **B.K. Kwon:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.06/D27

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DoD W81XWH-20-1-0480

Title: Predictors of intra-parenchymal hemorrhage progression in cervical spinal cord injury

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Abstract: Intraparenchymal hemorrhage (IPH) following acute spinal cord injury (SCI) is associated with poorer neurological outcomes. This study aimed to use serial MRIs to determine if routine clinical practices of mean arterial pressure (MAP) augmentation between 85-90 mmHg with the use of vasopressors and venous thromboembolism prophylaxis (VTEP) with the use of anticoagulants exacerbate IPH progression in acute SCI patients. 13 patients presenting with acute cervical SCI were enrolled in the ongoing CHASM trial (ClinicalTrials.gov: NCT04758377). MAP was kept between 85-90 mmHg with norepinephrine (NE) and was recorded every hour. VTEP was started at 49-68 hours for all patients. IPH was quantified on T2-weighted imaging taken at baseline (<24 hours post-SCI) and 2-, 4-, 7-, and 14-days post-SCI. Hemorrhage progression (delta IPH) was calculated between baseline-day 2 imaging, then from days 2-4, 4-7, and 7-14. Simple linear regression demonstrated a significant correlation between time-weighted average MAP (TWA-MAP) and delta IPH at days 2 and 4 ($p=0.0076$ and $p=0.0046$). A multilinear regression model accounted for 94-98% of the variance observed between TWA-MAP, NE dosage, baseline IPH, and time to initiation of VTEP. The amount of IPH on baseline MRI was the strongest factor influencing delta IPH within the first 4 -days post-SCI, as well as TWA-MAP. NE dosage and the time to initiation of VTEP were not found to be important predictors of delta IPH. These findings suggest that there may be a rationale for tailoring our hemodynamic management goals in patients who present with severe hemorrhage at the time of injury.

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Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.07/D28

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Canadian Institutes of Health Research - Canada Graduate Scholarship (Masters 2023-2024)
Canada Foundation for Innovation
Canada Research Chairs
University of Alberta - Walter H. Johns Graduate Fellowship
University of Alberta - Travel Award

Title: Epidural spinal cord stimulation may modulate ascending pathways of spinal circuitry after a motor complete spinal cord injury: A case study

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Abstract: Background/Objectives: Epidural spinal cord stimulation (eSCS) implanted at the T11-L1 regions of the spinal column, covering the lumbar enlargement of the spinal cord, has been used to restore some standing and stepping following a motor complete spinal cord injury (SCI) (Harkema et al., 2011). In this study, we assessed, for the first time, the effect of eSCS near the lumbar enlargement on ascending pathways. **Methods:** One participant (T2, AIS A, 7 years post-injury) had two implanted eSCS paddle leads centered on the T6 and T9 regions of the spinal column to relieve intractable pain. Using the more distally located paddle lead, we first conducted 3 sessions of epidural mapping with 16 channels of electromyography placed on the lower limbs and trunk. We subsequently recorded evoked movements in the legs, trunk, abdomen, and neck. **Results:** Very interestingly, we observed muscular targets that are associated with spinal circuitry well above the level of the applied eSCS. Specifically, stimulation through the distal paddle lead resulted in a retraction of the participant's neck, improving alignment over the thorax and allowing lateral movements of the head. Without eSCS through this lead, the participant's neck rests in a protracted position, preventing lateral movements of the head. The optimized program that improved the participant's functional ability to turn their neck was 10-15-2+7+13+ at 30 Hz and 1000 µs pulse width. The most comfortable change in neck function was observed between 10 mA-12.6 mA. **Conclusion:** This study, for the first time, provides quantitative evidence of an ascending influence of eSCS on the spinal circuitry. Furthermore, this study enhances our knowledge of propriospinal connectivity and helps delineate the eSCS benefits that arise above the level of injury after a motor complete SCI.

Disclosures: D.J. Mann: None. **J.A. Porter:** None. **M. Yuan:** None. **S.J. Harkema:** None. **V.K. Mushahwar:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.08/D29

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Natural Sciences and Engineering Research Council of Canada
Canada Foundation for Innovation
Faculty of Medicine and Dentistry Doctoral Fellowship
Canada Research Chairs

Title: Transcutaneous spinal cord stimulation modulates bimanual coordination

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Inst. for Smart Augmentative and Restorative Technologies and Hlth. Innovations (iSMART), Univ. of Alberta, Edmonton, AB, Canada

Abstract: The overarching goal of this project is to develop a rehabilitation intervention that combines activity-based therapy and non-invasive spinal cord neuromodulation to improve bimanual arm function after spinal cord injury. Cooperative bimanual arm movements are critical in daily life and facilitate the performance of numerous activities; however, most rehabilitation interventions for spinal cord injury currently focus on unimanual tasks. A recent study demonstrated that transcutaneous spinal cord stimulation (tSCS) improves unimanual arm function (Inanici et al, 2021) after chronic injury. In this study, we investigated the effect of tSCS on the kinematic performance of various types of arm movements. Neurologically-intact study participants sat in front of a bimanual KINARM exoskeleton and performed three visually-guided goal-directed movements (unimanual, bimanual common-goal and bimanual dual- goal). The movements were performed with and without the application of cervical tSCS. Each movement type was repeated 20 times, and reaction time, movement time and movement error were quantified to evaluate the kinematic performance in each task. Reaction time was the time the movement was initiated after the target was presented. Movement time was the time it took to reach the target once the movement was initiated. Movement error was the root mean square of the vertical deviation of the movement from a straight line connecting the home position and the target. In the absence of tSCS, bimanual dual-goal movements in which the two arms reached to two different targets simultaneously, had significantly longer movement time and larger movement error relative to unimanual movements and bimanual common-goal movements (i.e., movements requiring the cooperation of both arms to complete). Interestingly, in the presence of tSCS, movement time and movement error significantly decreased, but only for the bimanual common-goal movements. There was generally no effect of movement type or tSCS on reaction time. Cooperative bimanual tasks require the sharing of spatial location between the two hands and tSCS may play an important role in modulating cortical and proprioceptive activity. The finding that tSCS improved kinematic performance only in the bimanual common-goal movements suggests that tSCS may have a positive impact on proprioception, especially the sense of position. These findings are now under investigation in study participants with spinal cord injury. The outcomes collectively pave the way for enhanced upper extremity rehabilitation interventions for persons with neurological conditions.

Disclosures: B. Parhizi: None. **S. Allahgholiloo:** None. **V.K. Mushahwar:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.09/D30

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Canadian Institutes of Health Research
Canada Foundation for Innovation
Canada Research Chairs

Title: Cutaneous inputs in modulate spinal circuitry during transcutaneous spinal cord stimulation

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Abstract: Introduction The communication between the brain and the periphery is disrupted by damage to the spinal cord, leading to a loss of sensorimotor function. Spinal neuromodulation through non-invasive transcutaneous spinal cord stimulation (tSCS) may play an important role in rehabilitation after spinal cord injury (SCI) by activating previously inaccessible neural networks (Barss, Trevor S et al., 2022; Zhang et al;2021) Computational models suggest that tSCS acts through similar pathways as epidural spinal cord stimulation (Hofstoetter, U. S. et al., 2018); however, current research does not reflect the implication of cutaneous inputs in the context of tSCS. The aim of this study is to explore how cutaneous input impacts the outcomes of tSCS by manipulating the role of cutaneous input with a topical anesthesia cream. **Methods** Twelve neurologically intact study volunteers were recruited and tSCS was applied to the cervical region using DS8R stimulators (Digitimer, Welwyn Garden City, UK). The impact of the blocking cutaneous input was tested by measuring the current amplitude producing the first sensory perception of the tSCS (mA), the amplitude of maximum tolerance of tSCS (mA), and two-point discrimination (cm). These outcomes were studied under two types of topical creams applied to the back of the neck, each for 30 minutes: 1) Versapro sham cream (control), and 2) Benzocaine 20%, Lidocaine 10%, and Tetracaine 4% (BLT) cream to block cutaneous receptors. Furthermore, we measured the current amplitudes needed to generate comparable peak-to-peak spinal evoked potentials (SEP) in the biceps brachii muscle after the application of each cream to evaluate the neural excitability produced by tSCS at the cervical level of the spinal cord. **Results and Conclusion** The sensory perception threshold, maximum tolerance, and two-point discrimination results significantly increased after the application of BLT cream, indicating that the topical anesthesia cream reduced sensation at the level of the skin. Moreover, when we maintained SEP peak-to-peak amplitudes at a constant level, there was a significant increase in the current intensity needed to achieve the same amplitude of neurological response, demonstrating that cutaneous inputs contribute to spinal excitability as a response to tSCS. As a result, cutaneous inputs have a role in activating neural pathways to the spinal cord while using tSCS as a neuromodulator.

Disclosures: Z. Karamzadeh: None. **J.A. Porter:** None. **V.K. Mushahwar:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

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Program #/Poster #: PSTR338.10/D31

Topic: C.11. Spinal Cord Injury and Plasticity

Support: University of Alberta Hospital Foundation
University of Alberta - Faculty of Medicine and Dentistry 75th Anniversary Studentship
Canada Foundation for Innovation
Canada Research Chairs

Title: Comparing three different spinal cord stimulation modalities for restoring walking after spinal cord injury

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Abstract: Introduction Spinal cord injury (SCI) may cause severe disruption to body functions such as locomotion. Spinal cord stimulation (SCS) is a promising approach for restoring walking by reactivating locomotor networks below the injury. This study investigates the efficacy of three SCS modalities—epidural stimulation, intradural stimulation, and intraspinal microstimulation (ISMS)— with a focus on determining the most effective approach for eliciting natural walking patterns. By evaluating each modality independently, this work seeks to provide guidance for optimizing SCS techniques that enhance locomotor recovery following SCI.**Methods** We designed a 16-channel custom-tailored implantable electrode array for both epidural and intradural stimulation specifically for the cat lumbar enlargement. To ensure compatibility with the cat model, the array had a total thickness of 100 microns. For epidural and intradural stimulation, the array was placed over the dura mater covering the lumbar enlargement and subdurally covering the same region, respectively. ISMS involves the precise insertion of 16 microwires into the spinal cord to target locomotor-related networks in the ventral horn. Experiments were conducted in deeply anesthetized cats, which were placed in a sling that supported their head and trunk while the legs moved freely over an instrumented walkway. A unified controller paradigm was employed for the delivery of SCS across the 3 modalities. A custom MATLAB algorithm was used to control the stimulation and data collection which included ground reaction forces, angular joint velocity, and motion capture.**Results and Conclusion**Magnetic resonance images of the extracted spinal cord revealed no evidence of compression or distortion due to the intradural array or ISMS electrodes. Preliminary kinematic

data demonstrate that ISMS facilitates a near-normal, graded walking pattern involving 4 primary synergies (forward reach, downward extension, backward propulsion, upward flexion). Epidural and intradural stimulation primarily produce a 2-synergy walking pattern composed of backward propulsion and upward flexion that lack graded control. All SCS modalities produce weight-bearing movements; however, a comparison of the distance that can be walked using each modality has not yet been performed. Moreover, detailed analyses of the stimulation amplitudes and energy expenditure for each modality are needed. These preliminary results demonstrate the ability of ISMS to more precisely target the locomotor-related networks in the spinal cord, potentially achieving more natural and coordinated restoration of walking after SCI.

Disclosures: A. Arefadib: None. **S. Mirkiani:** None. **C. O'Sullivan:** None. **B.J. Holinski:** None. **N. Tyreman:** None. **V.K. Mushahwar:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.11/D32

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOD W81XWH-21-1-0551

Title: Novel preclinical assessment of spasticity in rodent forelimb following cervical spinal cord injury

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Abstract: Traumatic spinal cord injury (tSCI) is an unrelenting condition that causes irreversible changes in an individual's life. More than 90% of patients develop spasticity, characterized by involuntary muscle activation that significantly impairs movement and coordination of the extremities. During clinical testing, spastic muscles typically exhibit a velocity-dependent increase in muscle tone. Currently, methods to objectively quantify forelimb spasticity in rodents are lacking.Here, we developed two novel devices to measure spasticity in the elbow joint and the digits of rodent forepaws. Rats with chronic SCI (inflicted using the Infinite Horizon Impactor at 200 kdyn) at the cervical C4 level were utilized for evaluation of these devices. For the elbow joint, a custom-designed robotic arm was designed to passively extend the joint at precisely defined velocities and to measure the muscle’s resistance. Preliminary results indicated

that the resistance (13.25 ± 2.61 mN) was more than three times higher in a spastic elbow joint compared to baseline measurements before the injury (3.62 ± 1.64 mN; t-test, $p < 0.001$). Additional measurements confirmed velocity-dependent resistance in the spastic limb. Thus, extending the elbow at 400 degrees/s resulted in a higher resistance (18.44 ± 3.56 mN) compared to that seen at 100 degrees/s (13.25 ± 2.61 mN; t-test, $p < 0.01$). To assess muscle tone in finger flexor muscles, we designed an inflatable balloon device. Once the balloon was placed into the forepaw, the pressure of the balloon was measured during rapid inflation. Injured paws showed to have 5-15% higher resistance to pressure inflation, measured in mmHg. Animals were tested using the robotic arm and the balloon device starting two weeks post-injury and continuing bi-weekly until chronic spasticity at 4 weeks was detected. Serial examinations of the elbow stretch reflex at 400 degrees/s revealed an increase in peripheral muscle resistance over time following spinal cord injury (SCI). The measurements showed a baseline resistance of 3.7 ± 1.49, increasing to 6.83 ± 1.62 at four weeks post-SCI, and further rising to 19.34 ± 4.22 by eight weeks post-SCI. We implanted electrodes in the peripheral nerve and forearm muscle to assess the Hofmann Reflex (H-Reflex). The results confirmed the validity of the spasticity measurements, revealing a significant increase in the H-reflex in the SCI animals compared to the control uninjured animals. The two devices will be used to monitor the effect of therapeutic stimulation on forelimb spasticity after cervical tSCI providing objective biomarkers to assess forelimb muscle tone.

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Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.12/D33

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOD award: W81XWH-21-1-0551

Title: Comparative electrophysiological and functional monitoring of rodent forelimb spasticity following cervical spinal cord injury

Authors: *A. SADEGHI[1], R. L. MURPHY[2], I. MAROSSA[7], A. LIN[3], E. BIELER[1], R. B. ROBINSON[4], C. T. MORITZ[5], S. I. PERLMUTTER[6], C. P. HOFSTETTER[8];
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Abstract: Spinal cord injury (SCI) is a devastating condition that leads to permanent disability in those affected. SCI disrupts supraspinal pathways that normally inhibit intrinsic spinal circuits,

resulting in increased motoneuron excitability. This hyperexcitability, known as spasticity, is characterized by involuntary muscle contractions and significantly reduces both functionality and quality of life. Currently, there are limited therapies available to alleviate spasticity. A major limitation of existing research in this field is the absence of reliable quantitative biomarkers for monitoring spasticity, particularly in the forelimb. In this study, we developed both electrophysiological and functional biomarkers to assess spasticity in rodents after cervical SCI. Female Long-Evans rats underwent severe hemi-contusion SCI at the C4 level using an Infinite Horizon Impactor set at 200 kdyn. A custom-designed cuff electrode was implanted around the median nerve along with EMG electrodes in the ipsilesional forelimb muscles to evoke and monitor changes in the Hoffmann reflex (H-reflex) and Rate-Dependent Depression (RDD). For real-time stimulation and monitoring, subcutaneously implanted electrodes were connected to the TDT device through the head stage connector implanted on the skulls. We also developed two devices to assess muscle tone in rodent forelimbs. The first device mimics clinical velocity-dependent measurements of spasticity by evaluating the resistance to stretch during rapid elbow extensions of both 50 and 90 degrees, and at two velocities, 100 and 400 degrees per second. The second device, described by Marossa et al. in their abstract, is an inflatable balloon that expands at various airflow rates to measure resistance during passive digit extension. Electrophysiological recordings in awake animals, six weeks post-SCI, revealed a 2- to 3-fold increase in the H-reflex, and a loss of Rate-Dependent Depression (RDD) compared to the uninjured condition, which are accepted electrophysiological markers of spasticity. Measurements of forelimb muscle tone supported these findings, showing a significant increase in peripheral muscle resistance in the injured animals compared to controls (18.44 ± 3.56 mN vs. 3.56 ± 1.64 mN, respectively; t-test, $p < 0.05$). Furthermore, results from passive digit extension tests also demonstrated a similar increase, with movement resistance approximately 10% higher in chronic SCI conditions than in the uninjured state. We believe our novel rodent outcome measures provide an objective biomarker for forelimb spasticity that will facilitate research into this clinically-relevant pathology.

Disclosures: A. Sadeghi: None. **R.L. Murphy:** None. **I. Marossa:** None. **A. Lin:** None. **E. Bieler:** None. **R.B. Robinson:** None. **C.T. Moritz:** None. **S.I. Perlmutter:** None. **C.P. Hofstetter:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.13/D34

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Spinal Cord and Brain Injury Research Center Endowment #5

Title: Serum biomarkers in surgically treated degenerative cervical myelopathy patients

Authors: *C. C. WOLSH[1,2], W. M. BAILEY[3], M. DARABI[4], H. ARORA[4], J. C. GENSEL[3], H. F. FARHADI[4], H. KASHIF[1];
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Abstract: Degenerative cervical myelopathy (DCM) is the largest cause of spinal cord injury in adults. Decompression surgery is the standard treatment but surgery does not always result in a patient improvement. The goal is to identify serum based biomarkers that associate with the quality of functional recovery following surgery to appropriately recommend future patients as candidates for surgery treatment.Here, we have screened for markers of spinal damage in serum from DCM patients before receiving decompression surgery and 6 months after surgery. These markers include Glial fibrillary acidic protein (GFAP), Apolipoprotein E (ApoE), Neuron-Specific Enolase (NSE), Neurofilament Light Chain (Nf-L), Amyloid Beta Peptide (AB40, AB42) and others. Functional recovery is measured here by modified Japanese Orthopaedic Association scale (mJOA) score. We hypothesize that an increase in markers for neuronal damage before surgery will correlate to lower recovery rate and correlate to increased severity before surgery, as measured by mJOA. Utilizing a biomarker panel to predict functional recovery will help identify patients for surgical treatment. Eventually, these biomarkers may be utilized as a diagnostic tool to identify early signs of spinal cord damage in DCM as well as other spinal cord injuries. Serum based diagnostics will be more accessible to patients, allow earlier identification of disease so patients can get treatment as soon as possible, and aid physicians in recommending the correct treatment following spinal cord injury. Our goal is to eventually provide a non-invasive, accessible and cost-effective diagnostic tool that will facilitate earlier and more accurate prognosis of disease progression and treatment outcomes.

Disclosures: C.C. Wolsh: None. **W.M. Bailey:** None. **M. Darabi:** None. **H. Arora:** None. **J.C. Gensel:** None. **H.F. Farhadi:** None. **H. Kashif:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.14/Web Only

Topic: C.11. Spinal Cord Injury and Plasticity

Support: COBRE Grant P20-GM103642
PR Science & Technology Trust 2022-00125.

Title: Effect of cefazolin in the gut microbiome of female rats after spinal cord injury.

Authors: *L. H. PAGAN[1,2], M. E. SANTIAGO-GASCOT[3], S. OCASIO[4], J. M. SANTIAGO SANTANA[5], I. SALGADO[6], O. MARTÍNEZ GUZMAN[7], M. CACERES-CHACON[8], J. D.

MIRANDA[9];
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Abstract: Background & Objectives: Spinal cord injury (SCI) is a devastating pathological state causing motor, sensory and autonomic dysfunction. To date, SCI remains without viable treatment. After the injury, molecular events centered at the lesion epicenter create a repulsive and non-permissive environment. This newly hostile condition promotes inflammation, inhibits axonal regeneration, and locomotor progression. This burdensome scenario warrants a multifactorial approach in the development of viable treatment. The administration of Tamoxifen (TAM), a selective estrogen modulator (SERM), has shown to reduce cellular death and improve locomotor recovery after SCI. Nevertheless, the mechanisms behind which TAM can exert these neuroprotective events are unknown. We hypothesize that through the gut-brain axis, and the production of anti-inflammatory metabolites, the gut microbiome has an impact on the neuroprotective mechanisms behind TAM. **Methods**: Female rats received a moderate contusion at the thoracic (T10) spinal cord level using the NYU impactor device. To determine the association of the gut microbiome in the neuroprotective effects of TAM, rats were implanted with TAM pellets immediately after SCI. Fecal matter pellets were collected before the trauma, and 7, 14, 21 and 28 days after injury for DNA extractions and sequencing of 16S rRNA genes. Microbiota was analyzed using standard bioinformatic pipelines. However, the effect of antibiotic in rodents after surgery was first investigated. **Results**: The microbiota of naive animals changed with time, and animals treated with antibiotics after the surgery or SCI presented dysbiosis with significant changes ($p<0.05$) in the microbiota according to Two-Way ANOVA analysis. **Conclusion**: The dysbiosis after SCI, and heightened with antibiotics could affect the recovery time in rats. The management of this newly microbiome disbalance could be an alternate route towards a viable treatment for SCI.

Disclosures: L.H. Pagan: None. **M.E. Santiago-Gascot:** None. **S. Ocasio:** None. **J.M. Santiago Santana:** None. **I. Salgado:** None. **O. Martínez Guzman:** None. **M. Caceres-Chacon:** None. **J.D. Miranda:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.15/D35

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Christopher and Dana Reeve Foundation #001-ESTRIVE

Title: Standardized locomotor and sensory behavior changes in a graded contusive spinal cord injury model

Authors: *J. BASTIDAS[1], M. R. DETLOFF[2], L. JONES[3], M. A. BAPTISTA[4], T. HANANIA[1]; [1]Behavioral Pharmacol., PsychoGenics, Inc., Paramus, NJ; [2]Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [3]Thomas Jefferson Univ., Boulder, CO; [4]Christopher & Dana Reeve Fndn., New Jersey, NJ

Abstract: Spinal cord injury (SCI) is a neurological condition with a devastating impact on the quality of life of affected individuals. Despite current medical care advancements, individuals with SCI may endure decreased motor function, altered sensation, and a myriad of autonomic changes for many years following the initial injury. Valid, reliable and consistent SCI preclinical models are indispensable tools for advancing novel therapeutics that are both safe and effective in improving SCI outcomes.In collaboration with the Christopher and Dana Reeve Foundation, PsychoGenics validated a graded thoracic (T8) SCI contusion lesion model in female Sprague Dawley rats, employing a clinically relevant controlled lesion method (IH impactor) to produce four graded lesion severities. Rats underwent laminectomy followed by contusion SCI using impact forces of 170, 200, 250 Kdyn, or 250 Kdyn with a 3-second dwell time. Functional recovery was assessed over five weeks using standard locomotor tests (BBB locomotor rating scale, horizontal ladder test), and PsychoGenics' proprietary gait analysis system, NeuroCube®. Changes in mechanical and thermal sensation were evaluated using von Frey and Hargreaves' tests. Notably, parameters such as time for bladder function recovery, urinary/health complications, and body weights were also recorded overtime. The severity of SCI correlated with biomechanical values recorded at the time of impact, as well as with behavioral and histological parameters (lesion size, spared tissue). Remarkably, locomotor behavioral assessments demonstrated sensitivity in detecting lesions with differences as low as 30-50 Kdyn. Distinct patterns of locomotor recovery were observed across the four groups, with significant differences noted between injury severities based on BBB and ladder test performance. Hypersensitivity to mechanical stimuli was evident post-SCI when compared with baseline values and/or sham animals. Rats subjected to the most severe lesion (250Kdyn + 3 seconds dwell time) exhibited the most consistent and significant changes in sensation, as well as bladder function. Thus, we have developed an in vivo SCI platform to assess the efficacy of potential therapeutic interventions that encompasses comprehensive evaluations of general health, locomotion, and sensation.

Disclosures: J. Bastidas: A. Employment/Salary (full or part-time):; Psychogenics. **M.R. Detloff:** 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.; Axonis Therapeutics. **L. Jones:** F. Consulting Fees (e.g., advisory boards); Christopher and Dana Reeve Foundation. **M.A. Baptista:** None. **T. Hanania:** A. Employment/Salary (full or part-time):; Psychogenics.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.16/D36

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Characterization of the Mouse Spinal Ejaculation Generator

Authors: *E. V. BROWN[1], L. M. COOLEN[2];
[1]Kent State Univ., Kent, OH; [2]Biol. Sci., Kent State Univ. Sch. of Biomed. Sci., Program In Neurosciences, Kent, OH

Abstract: Nearly all men with spinal cord injury (SCI) have difficulty ejaculating without invasive medical intervention. The development of treatments is limited by an incomplete understanding of the underlying mechanisms of SCI-induced anejaculation. Ejaculation is a reflex completely controlled by a group of cells in the L3/L4 spinal cord called lumbar spinothalamic (LSt) cells which comprise the spinal ejaculation generator (SEG). Rat models of thoracic SCI have reliably recapitulated anejaculation, but genetic access to LSt neurons available only in mouse is necessary to further probe SCI induced changes to the ejaculatory system. While LSt cells exist in mice they have not yet been fully characterized, and it is unknown if mice exhibit SCI induced anejaculation. Here we provide a molecular characterization of mouse LSt neurons and begin to develop the mouse as a model of SCI induced anejaculation. First, using galanin immunostaining, the distribution and location of LSt neurons in mouse was confirmed to laminae VII and X in the L3-L4 spinal cord, similar to rat and human. Next, RNAscope was used to confirm the expression of the neuropeptides typical of rat LSt neurons: *galanin, GRP, CCK and pENK*. To determine the role of LSt neurons in ejaculation, we paired male mice with hormone primed, ovariectomized females and allowed them to interact normally before being euthanized and perfused after mating with or without ejaculation compared to males that did not mate (n=6-8/group). RNAscope against *galanin* and *cFos* was used to quantify the extent of LSt neuron activation following each behavior. Nearly 100% of LSt neurons expressed *cFos* following ejaculation, supporting the involvement of mouse LSt neurons in ejaculation. We next asked if, like in rat, dorsal penile nerve (DPN) stimulation can be used to experimentally induce ejaculatory reflexes. We recorded EMG from the bulbocavernosus muscle (BCM) following DPN stimulation and found a consistent response not typical of what is seen in rat. However, this BCM response was only seen following spinal transection, which indicates that supraspinal inputs inhibit these BCM responses consistent with DPN stimulation induced ejaculation in rat. Taken together, these data support the idea that mouse LSt neurons serve the same function as in rat and human and that the mouse can serve as a model to study experimentally induced ejaculation. Ongoing work is testing the extent to which SCI induces anejaculation in mouse.

Disclosures: E.V. Brown: None. **L.M. Coolen:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.17/D37

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life

Title: Electrophysiological Evidence of Spike Timing-Dependent Plasticity in the Awake Adult Rat

Authors: *S. GAIKWAD[1], Y. CHEN[2], W. BOGUE[1], T. M. VAUGHAN[2], J. S. CARP[2,3], M. OUDEGA[1,4,5,6], J. R. WOLPAW[2,3], M. A. PEREZ[1,7,4];
[1]Shirley Ryan AbilityLab, Chicago, IL; [2]Natl. Ctr. for Adaptive Neurotechnologies, Albany Stratton VA Med. Ctr., Albany, NY; [3]Department of Biomedical Sciences, State University of New York, Albany, NY; [4]Edward Hines Jr. VA Hospital, Hines, IL; [5]Department of Physical Therapy and Human Movement Sciences, Northwestern University, Chicago, IL; [6]Department of Neuroscience, Northwestern University, Chicago, IL; [7]Department of Physical Medicine and Rehabilitation, Northwestern University, Chciago, IL

Abstract: Principles of spike timing-dependent plasticity (STDP) have been used to restore motor function in people with spinal cord injury (SCI). The goal of the present study was to examine the effect of STDP neurostimulation targeting spinal motoneuron synapses in awake adult rats. Adult male and female Sprague Dawley rats were implanted with stainless steels screws through the skull over the hindlimb area of the left motor cortex to enable cortical stimulation. A custom-made cuff with embedded wire electrodes was placed around the right posterior tibial nerve to enable peripheral stimulation. Wire electrodes were placed into the soleus muscle to record motor evoked potentials (MEPs), H-reflex, and the maximal motor response (M-max) about 6 weeks post-surgery. During STDP, descending volleys evoked by cortical stimulation were timed to arrive at spinal motoneurons 2.5 ms before (STDP+) or 15 ms after (STDP-) arrival of antidromic potentials evoked by tibial nerve stimulation. Rats received 180 paired pulses every 10 sec for ~30 min and measurements were taken before (baseline) and up to 40 min after each stimulation session. We found that the MEP size increased by ~32% with STDP+ and decreased by ~27% with STDP- compared with baseline MEP size for up to 40 min after ending the stimulation. The effects of STDP on MEP size was recorded for up to 16 weeks post-surgery, which enables investigating long-term neurostimulation approaches. This study provides electrophysiological evidence for STDP at spinal cord motoneuron in awake adult rats using a stimulation principle similar as used in humans with SCI. The availability of an adult rat model of STDP stimulation may benefit studying approaches to further enhance recovery in people with SCI.

Disclosures: S. Gaikwad: None. **Y. Chen:** None. **W. Bogue:** None. **T.M. Vaughan:** None. **J.S. Carp:** None. **M. Oudega:** None. **J.R. Wolpaw:** None. **M.A. Perez:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

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Program #/Poster #: PSTR338.18/D38

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH (NINDS) Grant 1R21NS125496-01A1
Institutional University Research Committee (URC) Grant 00125691
Craig H. Neilsen Foundation Grant 999331

Title: Early changes in breathing predict pain after thoracic spinal cord injury in mice: possible reversibility with olfactory stimuli

Authors: A. CHUANG, S. HOCHMAN, *D. J. NOBLE;
Emory Univ., Atlanta, GA

Abstract: Spinal cord injuries (SCIs) frequently cause physical disability, regulatory dysfunction, and pain. Chronic pain typically emerges weeks after an injury, and its underlying mechanisms are complex and multifaceted. Further, it remains largely unknown why some individuals develop debilitating pain after an SCI and others do not. Predicting the onset of future pain after SCI would allow for earlier intervention and a better understanding of its etiology, and may lead to earlier therapeutic strategies that limit pain emergence. To discern whether early changes in important biological variables predict onset and severity of future pain, movement (activity) and respiratory rate (RR) of adult male and female mice were recorded before and at early time points after (1-3, 5, and 8 days) SCI using remote electric field sensors. These measures were then correlated with behavioral responses in tests of thermal and mechanical sensitivity four weeks post-injury. Mice exhibited sharp decreases in RR variability and movement immediately after injury, but these two early changes were not correlated with each other. Mice that moved the least immediately after injury became the most hypersensitive in the mechanical von Frey test. Mice that increased their RR variability within the first week after injury later preferred increased temperatures in the thermal preference test. Administration of two odorants - lavender and limonene - shortly after injury changed respiratory patterns and attenuated future pain responses. Overall, early changes in movement and RR variability may be predictive of future pain-related outcomes after SCIs, and modification of breathing with relaxing or rewarding olfactory stimuli has the potential to reduce pain-related behavior.

Disclosures: A. Chuang: None. **S. Hochman:** None. **D.J. Noble:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.19/D39

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CIHR
TransMedTech

Title: A rat model of contusive cervical spinal cord injury to develop neuroprosthetic intervention for fine motor function

Authors: *R. H. EL HASSAN[1], M. LABARRE[2], B. TOUVYKINE[2], L. FEROTIN[2], M. BONIZZATO[3];
[1]Ecole Polytechnique Montreal, Montreal, QC, Canada; [2]Polytechnique Montreal, Montreal, QC, Canada; [3]Electrical Engin., Polytechnique Montreal, Montréal, QC, Canada

Abstract: Spinal cord injury (SCI) has a global prevalence of 15.4 million individuals. Incomplete SCI leads to movement deficits within a broad spectrum of severities. Therapeutic approaches for SCI encompass surgical intervention, neurorehabilitation, and neurostimulation. In humans, upper cervical lesions commonly result in hand and arm extension deficits. However, limited research addresses restoring upper limb function in individuals with SCI. In the rat model, it is unclear how contusion severity differentially affects fine and gross forelimb function. In this study, we establish a contusive SCI model targeting fine motor function and characterizing deficits across varying SCI severities. 25 female Long Evans rats were divided into 5 groups: 1 sham and 4 experimental groups with contusion forces: 90, 95, 100, and 110kdyn at the left C3/C4 level. Animals underwent training for reaching/grasping pellets and treadmill walking, while untrained tasks included string pulling, cylinder wall touching, and ladder walking. We recorded rats at baseline and for 8 weeks post-injury. Assessment metrics consisted of: success rate in reaching, movement kinematics on the treadmill and during string pulling, missteps on the ladder, and the ratio of left/right touches in the cylinder. Following SCI, mean success rates in the reaching task dropped significantly from a baseline of 50% to 35% in the 90 kdyn group, 23% in the 95 kdyn group, 17% in the 100 kdyn group, and 6% in the 110 kdyn group ($p < 0.05$). Animals across experimental groups did not exhibit notable deficits or dragging during treadmill locomotion. In the cylinder task, the number of left touches decreased mainly in the highest injury group (110kdyn), although all groups recovered to near-baseline ratios over time. Lastly, injured rats missed more steps while crossing the ladder. Our findings indicate particular sensitivity of the reaching task for studying fine motor deficits after moderate lesions, whereas performance in the remaining tasks is only impacted by severe lesions. Our model provides a robust framework for task and injury level selection, essential for the development and assessment of neuromodulation interventions in the rat model of SCI. It minimizes the need for extensive testing on a large number of rats before initiating studies on contusive lesions, optimizing efficiency and reducing the requisite number of animals for experimentation. Our model focuses on cervical injuries to assess hand motor functions, opening doors for novel neuromodulation interventions such as motor cortex and spinal stimulation for alleviating SCI deficits.

Disclosures: R.H. El Hassan: None. **M. Labarre:** None. **B. Touvykine:** None. **L. Ferotin:** None. **M. Bonizzato:** Other; Cofounder of 12576830 Canada Inc., a startup company working on cortical stimulation and submitted a related patent application (PCT/CA2020/051047).

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.20/D40

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Institut universitaire de France (IUF)
Association Demain debout -Aquitaine
Association verticale

Title: Longitudinal analysis of sensorimotor, social and anxiety-related behaviors in mice over aging, and after spinal cord injury : the influence of protocol design in behavioral assessment

Authors: *C. M. GAZARD[1], Y. N. GERBER[2], F. E. PERRIN[3,4];
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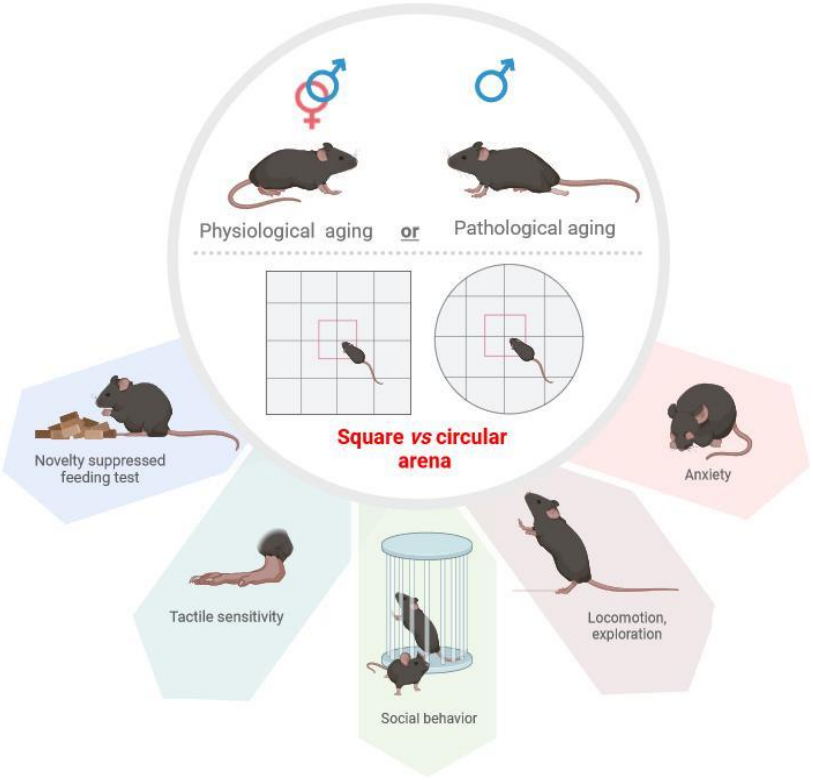
Abstract: Behavioral tests have been utilized for years to assess the functioning of the central nervous system and its alterations. Among these tests, the open field test stands out as a commonly employed method to gauge murine behavior, notably exploration, spontaneous motor activity, and manifestations of stereotyped and anxiety-like behaviors. Various shapes and sizes for the experimental design of open field arenas have been reported in previous studies, selected either to align with specific research goals or to streamline data collection and analysis procedures. In our investigation, we explored the effect of the shape of the open field arena on mouse behavior across physiological aging, considering age and sex as variables. Additionally, we examined how the shape of the open field influences the behavior of male mice following spinal cord injury in an age-dependent manner. Our findings revealed gender disparities in tactile sensitivity and anxiety levels across physiological aging, as well as a direct link between open field shape and motor activity, tactile sensitivity, and social behavior. Moreover, we observed an effect of the shape of the arena on social behavior after spinal cord injury in male mice. Our data underscore the significant influence of shape of the arena on mice behaviors, and highlight the critical role of experimental protocol design in behavioral assessments.



Disclosures: C.M. Gazard: None. **Y.N. Gerber:** None. **F.E. Perrin:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.21/D41

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Department of Defense W81XWH1810675
Kentucky Spinal Cord Head Injury Research Trust, Grant #17-5

Title: Effects of chronicity and severity on bowel function after spinal contusion in male rats

Authors: *B. PEREZ DE CORCHO VAZQUEZ[1], J. FELL[1], R. F. HOEY[2], D. MEDINA AGUINAGA[3], C. HUBSCHER[4];
[1]Anatom. Sci. & Neurobio., Univ. of Louisville Anatom. Sci. & Neurobio., Louisville, KY; [2]Anatom. Sci. and Neurobio., MetroHealth Syst., South Euclid, OH; [3]Anatom. Sci. and Neurobio., Univ. of Louisville Anatom. Sci. and Neurobio., Louisville, KY; [4]Dept Anatom. Sci. & Neuro, Univ. of Louisville Anatom. Sci. & Neurobio., Louisville, KY

Abstract: Spinal cord injury (SCI) disrupts neural pathways between the central and peripheral nervous system impacting many body systems including the bowel. The high occurrence of bowel-related issues often leads to rehospitalization, affecting morbidity and quality of life of individuals with SCI. In humans, SCI leads to various functional changes that collectively disrupt the ability of the gastrointestinal tract to store and evacuate efficiently. The mechanisms behind these deficits, however, are not well understood. In the present study, a clinically relevant rodent T9 contusion model with graded injury severities (mild, moderate, and severe) at different timepoints post-injury (acute, sub-acute, chronic) was utilized to examine SCI induced bowel dysfunction. Outcome measures included both external anal sphincter electromyography (EAS-EMG) and anorectal manometry, which is used in clinical settings to assess colonic dysfunction in individuals with SCI. Significant differences were found in EAS response latency and/or duration of contractile activity in terms of chronicity and severity of SCI. Frequency of giant contractions in contrast was quite variable across individual animals within groups. The findings to date illustrate unique changes in bowel function following incomplete SCI in a preclinical model, providing insights for developing improved clinical strategies, and further validating rodents as a model for SCI induced bowel dysfunction.

Disclosures: B. Perez de Corcho Vazquez: None. **J. Fell:** None. **R.F. Hoey:** None. **D. Medina Aguinaga:** None. **C. Hubscher:** None.

Poster

PSTR338: Spinal Cord Injury: Animal Models and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR338.22/D42

Topic: C.11. Spinal Cord Injury and Plasticity

Support: This work is funded by the Daniel and Ada Rice Foundation

Title: Inflammatory and locomotor changes associated with sensory phenotypes of neuropathic pain after spinal cord injury

Authors: *B. AVONTS[1], D. KIM[2], D. GARCIA PRADA[2], R. G. FESSLER[2], B. T. DAVID[3]; [1]Neurosurg., Rush Univ. Med. Ctr., Chicago, IL; [2]Rush Univ. Med. Ctr., Chicago, IL; [3]Neurolog. Surgery, Rush Univ. Med. Ctr., Chicago, IL

Abstract: Central neuropathic pain (CNP) commonly develops in individuals after spinal cord injury (SCI), causing debilitating symptoms and sensory abnormalities to mechanical and thermal stimuli. The biological variability of pain phenotypes in these individuals has limited the number of positive outcomes. Thus, it is necessary to investigate the physiological processes contributing to sensory changes that develop over time. Using the tail flick and von Frey tests, we performed hierarchical clustering to determine the subpopulation of rats that developed thermal and mechanical sensory abnormalities. To measure inflammation as a potential mediator of CNP phenotypes, we used flow cytometry and immunohistochemistry. Lastly, to assess the

secondary effects on locomotor recovery, up to 8 weeks after injury, we used the CatWalk test to assess multiple parameters of gait. The von Frey test showed a subpopulation of SCI rats which were hyposensitive to mechanical stimuli from 6-8 weeks following injury. The tail flick test showed a subpopulation of SCI rats that were hypersensitive to thermal stimuli at 1 week and 3-8 weeks after injury. Rats with both subtypes of mechanical normosensitivity and thermal hypersensitivity showed an increase in the percent of macrophages at the injury epicenter 8 weeks following injury. The results also showed a significant change in locomotor recovery between rats with and without sensory abnormalities, with the greatest impairment shown in the mechanical normosensitive and thermal hypersensitive subgroups which displayed elevated immune cells. This research offers insights into the complex physiological outcomes of SCI, particularly focusing on the inflammatory cells associated with the development of CNP and its implications on locomotor recovery. Further investigation into acute inflammatory cells may be insightful for predicting the development of pain phenotypes.

Disclosures: B. Avonts: None. **D. Kim:** None. **D. Garcia Prada:** None. **R.G. Fessler:** None. **B.T. David:** None.

Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR339.01/D43

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS R01NS114279 (Thompson)
South Carolina Spinal Cord Injury Research Fund (#2019 PD-01, #2021 PD-01, Thompson)
the Doscher Neurorehabilitation Research Program (Thompson)
NICHD P2CHD086844 (Kautz)

Title: Cortical map representation of corticospinal excitation and inhibition for the tibialis anterior in people with and without chronic incomplete spinal cord injury

Authors: *R. COTE, A. M. PHIPPS, A. K. THOMPSON;
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Abstract: Motor evoked potential (MEP) to transcranial magnetic stimulation (TMS) is frequently used as a measure of corticospinal excitability and plasticity in neurorehabilitation studies. While cortical representation of MEP is often examined, cortical representation of its silent period (SP) that reflect corticospinal inhibition, at least partly, remains largely unknown. Thus, to understand representation of corticospinal excitation and inhibition in health and in chronic CNS injury, we obtained cortical MEP and SP maps for ankle dorsiflexor tibialis anterior (TA) in adults with foot drop due to chronic incomplete spinal cord injury (SCI) and adults without SCI.

Thirteen adults with chronic (1-17 yrs post) incomplete SCI and 11 adults without neurological conditions were studied. MEPs were elicited in the TA of the more affected leg (SCI) or the right leg (non-SCI), using a custom-made bat-wing coil with radii of 9cm, while the sitting participant maintained the isometric TA EMG activity at ≈30% maximum voluntary contraction level. In each participant, active MEP threshold was estimated at the tentative hot spot prior to mapping, and an TMS intensity of 110-115% active threshold was used for the entire mapping procedures. Four pulses of TMS were applied at each of the 42 locations over -3 to +3cm posterior to the vertex and -1 to +4cm contralateral to the side of the leg studied. Peak-to-peak MEP and SP duration (from the onset of MEP to the return of EMG activity to the peristimulus level after MEP) were measured.
When we averaged MEP maps and SP maps across all participants, the average hotspots were found 1cm posterior and 1cm lateral to the vertex for both MEP and SP. However, at individual level MEP and SP hotspot differed in no particular directions by ≈2.0cm in both non-SCI and SCI. This suggests that cortical map representation of corticospinal excitation differs from that of inhibition. When we calculated >75% peak response areas, MEP (excitation) representation area appeared smaller in SCI (19±8% of the total mapped area) than in non-SCI (23±13%), although the difference was not statistically significant ($p=0.13$ by t-test). >75% peak SP (inhibition) representation area was 28±14% of the total mapped area in SCI and 30±14% in non-SCI, not different between the groups ($p=0.41$). >75% peak response area seemed to be larger for SP than MEP, but the difference was not statistically significant ($p=.061$ by two-way mixed model ANOVA). Additional data collection and further analyses are currently ongoing to better understand the relationship between cortical representation of corticospinal excitation and inhibition in people with and without SCI.

Disclosures: R. Cote: None. **A.M. Phipps:** None. **A.K. Thompson:** None.

Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR339.02/D44

Topic: C.11. Spinal Cord Injury and Plasticity

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South Carolina Spinal Cord Injury Research Fund SCIRF #2022 PD-01, #2021 PD-01, #2019 PD-01)

Title: Operant conditioning of the tibialis anterior motor evoked potential (MEP) in people with foot drop due to chronic incomplete SCI: MEP and silent period

Authors: *A. K. THOMPSON, R. K. COTE, A. F. LEWIS, K. FJELD, B. DELLENBACH, A. M. PHIPPS;
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Abstract: After spinal cord injury (SCI), corticospinal excitability diminishes, resulting in weak voluntary activation of muscles below the injury and impaired motor control. However, such deficits are reversible at least partially. Operant up-conditioning of the motor evoked potential (MEP) to increase corticospinal excitability may improve the activation of the targeted muscle and improve motor functions in which that muscle participates in people with SCI (J Neurophysiol 2018:120:2745-60; 2019:121:853-66). To understand neurophysiological mechanisms of MEP up-conditioning, we are examining changes in tibialis anterior (TA) MEP and its silent period (SP), which reflects cortical inhibition, at least partly, over 24 sessions of MEP up-conditioning or simple MEP elicitation (control protocol) in people with foot drop due to chronic incomplete SCI. Adults with chronic (>1 yr post SCI) stable incomplete SCI are studied with 6 baseline and 24 up-conditioning or control sessions over 10 weeks. In all sessions, 225 TA MEP trials are administered at ~10% above active threshold intensity of transcranial magnetic stimulation while the participant maintains ~30% maximum voluntary contraction (MVC) level of TA EMG activity. During baseline and control sessions, MEPs are simply measured with no feedback on MEP size. During conditioning trials of the conditioning sessions, the participant is encouraged to increase MEP size and is given immediate feedback as to whether MEP was larger than a criterion. MVC, MEP size, and SP duration are compared between the 6 baseline and the last 6 conditioning/control sessions. With the up-conditioning protocol (N=12), MVC changed by +11±6%, MEP by +44±6%, and SP by -23±6%; whereas with the control protocol (N=6), MVC changed by +24±9%, MEP by +17±16%, and SP by +18±8%. When SP-to-MEP ratio (indicating the balance between corticospinal inhibition and excitation) was calculated, it was decreased consistently with up-conditioning (-45±5%) but not with control (+9±15%), indicating that the decrease of corticospinal inhibition is specific to MEP up-conditioning. To understand the potential link between SP changes and function improvements, further studies and analyses are currently underway.

Disclosures: A.K. Thompson: None. **R.K. Cote:** None. **A.F. Lewis:** None. **K. Fjeld:** None. **B. Dellenbach:** None. **A.M. Phipps:** None.

Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

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Program #/Poster #: PSTR339.03/D45

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 5R01NS111234
5R01NS111234-04S1
5R01NS111234-04S2

Title: Persistent inward currents in spinal sensory neurons associated with the presence of spinal cord injury-related neuropathic pain

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Abstract: Chronic spinal cord injury (SCI) causes spinal networks below the lesion to reorganize, leading to maladaptive sensorimotor consequences. Among these conditions, SCI-induced hyperexcitability of spinal sensory networks can lead to SCI-related neuropathic pain (SCI-NP). SCI-NP is often marked by the presence of allodynia–pathologically reduced thresholds for recruiting spinal nociceptive networks–and hyperalgesia–amplified and/or prolonged responses to overtly painful stimuli. A lowered threshold for spiking, an increased input-output relationship, and self-sustained firing are all hallmarks of membrane dynamics shaped by an increased influence of excitatory persistent inward currents (PICs), suggesting that some core features of SCI-NP may be attributable to this mechanism. PICs are non-inactivating flux of positive ions mediated by voltage gated sodium and calcium channels coupled to membrane-bound G protein receptors. In motoneurons, PICs are facilitated by dendritic serotonin and norepinephrine receptors; in sensory neurons, metabotropic glutamate receptors. The role(s) of PICs in SCI-NP has only been preliminarily characterized. Here, we test the hypothesis that spinal sensory neurons in rats with SCI-NP will exhibit firing dynamics consistent with an increased influence of PICs compared to those that lack signs of SCI-NP and to neurologically intact rats. Using microelectrode arrays, we recorded multi-unit neural activity *in vivo* from the spinal lumbar enlargement of adult male Sprague-Dawley rats either with or without chronic SCI and SCI-NP. Multi-unit neural activity was decomposed offline and single neurons were functionally classified based on changes in their firing rate during mechanical probing of their peripheral receptive field. PIC firing dynamics were identified via the archetypal nonlinear firing pattern and the presence of self-sustained firing after sensory feedback was withdrawn. We further characterized PIC-like firing dynamics using features developed for motoneurons, including acceleration slope, attenuation slope, brace height, and duration of afterdischarge. All procedures were approved by the IACUC of Washington University in St. Louis. We find that PIC-like firing patterns are more prevalent in spinal sensory neurons of rats with SCI-NP than those that lack SCI-NP and neurologically intact rats. Additionally, estimated PIC magnitude and duration of self-sustained firing were greater in rats with SCI-NP than those without. This suggests the sensory hyperexcitability associated with SCI-NP may be related in part to aberrant PICs secondary to disrupted neuromodulatory drive below the lesion.

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Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

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Program #/Poster #: PSTR339.04/D46

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 5R01NS111234
5R01NS111234-04S1
5R01NS111234-04S2

Title: Features of asynchronous local field potential activity vary across structural and functional boundaries of spinal networks and are altered by spinal cord injury

Authors: *G. N. MORENO ROMERO[1,2], M. F. BANDRES[1,2], J. G. MCPHERSON[1,2,3,4,5]; [1]Biomed. Engin., [2]Program in Physical Therapy, [3]Anesthesioogy, [4]Pain Ctr., [5]Neurosci., Washington Univ. in St. Louis, St. Louis, MO

Abstract: It is widely recognized that synchrony between local field potentials (LFPs) across temporal, frequency, and spatial domains is associated with information transfer in supraspinal networks. Specific features of oscillatory activity have also come to define certain structural and functional brain regions. However, oscillations are generally transient - lasting from tens to a few hundred milliseconds at a time. As such, they represent only a small fraction of overall LFP activity. Indeed, the bulk of this activity is asynchronous. There is also evidence that asynchronous neural activity varies across regions of the brain and with brain state, perhaps representing yet another substrate for network organization or information transfer. In comparison to the brain, little is known about LFP activity in the spinal cord. Here, we ask whether asynchronous LFP activity varies across structural and/or functional regions of the of the spinal cord and whether these features change when ascending/descending pathways are compromised by injury. We focus on the lumbar enlargement, which subserves a multitude of sensorimotor and autonomic functions and whose functional organization is closely related to its structural organization.All experiments were approved by the WUSTL IACUC. This study included 5 neurologically intact rats, 5 rats with chronic SCI-related neuropathic pain (SCI-NP), and 5 rats with chronic SCI that lacked neuropathic pain (all adult male Sprague-Dawley). SCI was induced via a T8/T9 midline contusion and a terminal electrophysiological experiment was conducted 6-8 weeks afterwards. Under anesthesia, a microelectrode array was implanted into the spinal cord at L5 dorsal root entry zone and extracellular neural recordings were gathered throughout the dorsoventral extent of the spinal gray matter. We found that broad spectrum intraspinal LFP power varies with anatomical in the spinal cord in all cohorts. For neurologically intact rats and rats with SCI that lack SCI-NP, power generally increased from the sensory-dominant dorsal horn to the motor-dominant ventral horn. Rats with SCI-NP were more variable, often with increased power in the intermediate gray matter compared to the dorsal or ventral horns. We also found that band limited LFP power was differentially modulated across depths, with higher frequency power increasing more across regions than lower frequency power in neurologically intact rats and rats without SCI-NP, whereas rats with SCI-NP tended to show more modulation of lower frequency power. These findings indicate that asynchronous neural activity does vary across spinal networks and may be related to network (dys-)function.

Disclosures: G.N. Moreno Romero: None. **M.F. Bandres:** None. **J.G. McPherson:** None.

Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

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Support: NIH Grant R01NS111234
NIH Grant 3R01NS111234-04S1
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Title: Ventral intraspinal microstimulation suppresses nociceptive transmission through a noradrenergic-dependent mechanism

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Abstract: Spinal cord injury (SCI) is a highly debilitating condition affecting nearly every system in the body. Among the consequences are movement impairments, autonomic dysreflexia, bowel, bladder and sexual dysfunction, and central neuropathic pain. SCI-related neuropathic pain has been attributed to pathologically overactive spinal responsiveness to sensory feedback due to an imbalance between excitatory, inhibitory, and neuromodulatory networks. Spinal cord stimulation holds promise for improving both movement impairments and neuropathic pain resulting from SCI. To this end, we have recently demonstrated that intraspinal microstimulation (ISMS) delivered to spinal motor pools below an SCI can simultaneously enhance motor output while reducing nociceptive transmission. However, the mechanisms by which ISMS elicits this dual effect remain unclear. Descending monoaminergic pathways are potent regulators of spinal motor and sensory excitability, with norepinephrine in particular playing a key role in inhibiting nociceptive transmission. Thus, here we investigated whether noradrenergic transmission is involved in the antinociceptive effects of ISMS. Using microelectrode arrays, we performed multiunit electrophysiological recordings in vivo in neurologically intact rats and in rats with chronic SCI. We recorded neurons at the L5 spinal segment receiving innervation from the plantar surface of the hindpaw. We tested the efficacy of our ISMS protocol in reducing nociceptive transmission when noxious stimulation was delivered to the peripheral receptive field. The same protocol was repeated in the presence of the α2-adrenergic blocker and inverse agonist RX821002 and changes in the antinociceptive effect of ISMS were assessed. As previously shown, ISMS was effective in depressing spinal nociceptive transmission, but only when the conditioning stimuli were combined with simultaneous activation of high threshold nociceptive primary afferents. Stimulation alone or combined with activation of low threshold cutaneous afferents did not alter spinal responsiveness to noxious sensory feedback. In addition, the antinociceptive effects of ISMS were abolished by blocking noradrenergic α2 receptors. Finally, we found that intrathecal RX821002 alone reduced spinal responsiveness to noxious sensory feedback - contrary to the current understanding of its actions. Although these results indicate a role for noradrenergic α2 receptors in the actions of ventral

ISMS, it is unclear whether these actions are mediated by α2 receptors on local spinal neurons or α2 receptors on descending coeruleospinal projection neurons.

Disclosures: J. Lucas-Romero: None. **M.F. Bandres:** None. **J.G. McPherson:** None.

Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: 5R01NS111234
5R01NS111234-04S1
5R01NS111234-04S2

Title: Altered features of spontaneous action potential discharge exacerbate inappropriate sensorimotor integration in networks below a spinal cord injury

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Abstract: Spinal sensorimotor integration is shaped by spontaneous action potential discharge (spAP) that occurs regardless of the presence or absence of overt descending, afferent, or segmental inputs. Spinal cord injury (SCI) causes a dramatic structural and functional reorganization of neural networks below the lesion and results in inappropriate sensorimotor integration. It is unknown whether SCI alters spAP and if any such alterations could exacerbate inappropriate sensorimotor integration. Here, we characterize spAP in vivo in spinal networks of neurologically intact rats and in spinal networks of rats with a moderate to severe chronic SCI, including in rats that also developed SCI-related neuropathic pain (SCI-NP). All experiments were approved by the Institutional Animal Care and Usage Committee at Washington University in St. Louis. The study included 18 neurologically intact adult male Sprague-Dawley rats and 14 rats with chronic SCI (T8 contusion), of which 7 had SCI-NP. spAP was recorded from microelectrode arrays implanted into the spinal cord at the L5 dorsal root entry zone. Electrode arrays spanned the dorso-ventral extent of the graty matter, enabling simultaneous characterization of spAP in sensory-dominant, motor-dominant, and integrative networks. Analyses included outcomes for both single and multi-unit neural data. Our primary outcome measures for single unit analyses included the number of neurons exhibiting spAP, temporal features of spAP (e.g., mean discharge frequency, regularity, burstiness), and the spatiotemporal profile of spAP across differing structural and functional regions of the gray matter. For multi-unit analyses, our primary outcome was temporal variability of spAP. We find that the proportion of nociceptive specific neurons exhibiting spAP, but not the total number of neurons

of all kinds exhibiting spAP, is associated with SCI-NP. We also find that the discharge rate of spontaneously active nociceptive specific neurons is higher in rats with SCI-NP than rats with SCI that lack SCI-NP and neurologically intact rats. By comparison, measures of the burstiness and regularity of individual spike trains were similar across all cohorts, while the variability of multi-unit activity was lower in rats with SCI than neurologically intact rats, particularly in the sensory-dominant dorsal horns. These findings indicate that spAP is altered following SCI and may contribute to inappropriate sensorimotor integration both by potentiating spinal nociceptive transmission and by constraining the patterns of activity spinal networks can produce.

Disclosures: M.F. Bandres: None. **J.G. McPherson:** None.

Poster

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Institut Carnot Leti

Title: Braingpt: learning the natural language of the human brain for neuroprosthetic applications

Authors: *I. SAKR[1,2,3,4], B. VAN DELFT[5], T. COLLIN[2,3,4], F. MARTEL[6], V. SPAGNOLO[2,3,4], A. GALVEZ[2,3,4], T. AKSENOVA[6], J. BLOCH[2,3,4], G. COURTINE[2,3,4], A. ALAHI[7,2], H. LORACH[2,3,4];
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Abstract: Brain-computer interfaces rely on the extraction and interpretation of brain activity to control a wide variety of effectors. Despite the growing amount of neurophysiological data collected globally, classical machine learning methods relying on human supervision fall short of delivering robust and transferable models for clinically relevant applications. Here we present BrainGPT, a new method inspired by natural language processing and computer vision that leverages unlabeled brain activity to extract efficient and generic neural features transferable across tasks and time. We used this method to significantly improve performance in brain decoding paradigms while reducing the amount of required labeled data. We quantified the benefits of this feature extraction method in different BCI tasks, across time. Finally, we demonstrated the efficacy of BrainGPT in real-time scenarios by decoding online upper limb movement attempts in a patient with spinal cord injury. This work offers new insights into the structure of brain activity that can be captured through self-supervised learning and opens the door to large brain language models (BLMs).

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Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

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Program #/Poster #: PSTR339.08/D50

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ET HARVEY AWARD
EIC-Transition-ReverseParalysis
.NeuroRestore

Title: A fully implantable brain-spine interface for lower limbs rehabilitation in patient with severe spinal cord injury

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Abstract: A spinal cord injury (SCI) interrupts the communication between the brain and the spinal cord, resulting in sensory, autonomic and motor deficits below the level of the lesion. Applying electrical epidural stimulation (EES) over the lumbosacral region of the spinal cord can reactivate the dormant, yet functional, motor neurons that control lower limb muscles and produce walking. In the context of the STIMO-BSI study (NCT04632290), a patient with chronic SCI, who had already undergone EES assisted neurorehabilitation, was implanted with 2 electrocorticogram (ECoG) devices to establish a digital bridge between the brain and the stimulation system implanted over his spinal cord. The study represents a proof of concept of the implementation of the BSI. In a new clinical study (Think2Go, NCT0624395) we evaluate the effectiveness of the fully-implantable Brain-Spine Interface in patients with severe chronic SCI who had not undergone EES neurorehabilitation before. We implant one WIMAGINE® device (64 ECoG electrodes) over the leg sensorimotor cortical area, paired with the purpose built ARC^{IM} lumbar system (Onward medical). The brain signals are wirelessly streamed and decoded in real-time through classification algorithms, which generate online predictions of motor intentions. We are able to classify motor attempts of different lower limb joints with high accuracy. The decoded predictions are then translated into electrical stimulation commands and wirelessly delivered to the neurostimulator targeting the dorsal roots of the spinal cord, with a latency of below 1 second and allowing safe and long-lasting prosthetic use of the BSI. Within the first 2 weeks after implantation and recovery, we were able to calibrate the full BSI. The participant used the system during 3 months of rehabilitation during which we were able to evaluate the effectiveness of the BSI as a neuroprosthesis through the comparison between BSI^{ON} and BSI^{OFF} conditions in different clinical tests. The participant, who had been intensely training for 2 years after the injury prior to the clinical trial, showed improved motor performance using the BSI, as well as when the BSI was turned off. Here we confirm the safety and effectiveness of the BSI system as a neuroprosthesis and in supporting functional recovery in an individual suffering from severe chronic SCI.

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Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

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Program #/Poster #: PSTR339.09/D51

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant (NINDS Award Number R01NS115877)
Minnesota SCI and TBI Research Program (2022 award contract: 214556; 2021 award contract: 191542)
Abbott for providing stimulation equipment and support.

Title: Exploration of computational methods for motor activity threshold detection during epidural stimulation parameter optimization to enable motor function in persons with spinal cord injury.

Authors: *K. A. FERNANDEZ[1], A. J. ASP[2], A. R. THORESON[2], M. L. GILL[2], D. D. VEITH[2], M. B. LINDE[2], J. M. HAGEDORN[3], M. A. BENDEL[3], D. G. SAYENKO[6], K. D. ZHAO[2,4], P. J. GRAHN[2,5];
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Abstract: Epidural stimulation (ES) is an FDA-approved therapy for pain syndromes and is under off-label investigation to enable lower extremity motor function in persons with spinal cord injury (SCI). Parameter optimization during ES sessions utilizes surface electromyography to quantify ES-evoked lower extremity muscle activity. Effort is focused on identifying ES amplitudes at motor activation threshold, and amplitudes that activate spinal reflexes as

determined by suppression evoked by doublet pulses applied during the reflex refractory period, 25-100 ms apart. Most ES threshold detection methods utilize amplitude-based methods that extract peak-to-peak (P2P) values of evoked responses, however, these strategies are prone to false positives. As preliminary work to identify more accurate motor activity threshold detection methods to improve parameter optimization, we explored if specific signal features altered detected ES threshold. Thus, we compared the P2P method to the Teager Kaiser Energy operation (TKEO) which detects instant frequency and amplitude changes. We hypothesized that detected ES thresholds significantly differ between the P2P method and the TKEO approach using different scalars (*j*), and that suppression ratios significantly differ.
Twelve participants (11 males) with SCI (10 motor complete) were implanted with bilateral percutaneous octrodes targeting the lumbosacral spinal cord. A train of five doublets (symmetric, biphasic, 250 µs pulse width, 0.5 Hz, 50 ms interpulse interval) were delivered every five seconds at ES amplitudes from 0.25 to 15 mA to participants in a relaxed supine position using patterned electrode configurations. ES threshold was determined when both conditions were first met for the P2P method: P2P signal amplitude larger than 50 µV and 2 standard deviations above the baseline signal. For the TKEO approach using 3 successive level scalar values, ES thresholds were determined when the TKEO output was first above 0.01, 0.1, and 1 standard deviation above the baseline signal.
ES thresholds and suppression ratios significantly differed across the P2P method and at least one TKEO *j*-value for most muscles and electrode configurations tested ($p < 0.05$; Friedman's test, Dunn's post hoc tests). These results indicate detected ES threshold and subsequent suppression ratios may be influenced by various signal features across detection methods which may result in use of suboptimal electrode configurations. Future work will explore how various techniques alter detected ES threshold and subsequent parameter optimization as well as data comparability within and across ES clinical trials to enable motor function after SCI.

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Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR339.10/D52

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Drexel CNHP Dean's R3 grant
NIH Grant RO1 NS097880

Title: Disruption of yield following contusive spinal cord injury - impacts on walking in challenging environments.

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Abstract: Approximately 40% of people with spinal cord injury (SCI) have incomplete injuries and are able to walk. Despite this, these individuals continue to have limited community ambulation due to gait instability during limb loading or yield in stance especially in more challenging environments (uneven terrain, slopes, compliant surfaces). Currently, there are few successful interventions that address yield impairments, and those that do focus on simple environments such as level, firm surfaces. Demands on yield change with more challenging terrains so understanding the impact of these environments on impaired yield following SCI is important to improve community ambulation. Adult, female Wistar, rats were trained to walk overground (OG) and bipedally on a treadmill (TM) on level and declined surfaces (up to -20°), and hindlimb kinematic data was collected preSCI on OG and TM on 0° (level), -10°, and -20° (declines). Rats then underwent a mid-thoracic spinal cord contusion at 175 kdyn with the infinite horizon (IH) device. PostSCI kinematic data was collected at 2-, and 6- weeks post SCI and compared to each rat's preSCI data on each task. Data were also compared within each time point for the different slopes (0° v -10° v -20°). In agreement with previous literature, we found that in the uninjured rat the ankle was more flexed and showed greater yield on -20° compared to 0° OG. There were also differences in angular velocity with the dynamic ankle angular velocity (degrees/sec^2 at touchdown - degrees/sec^2 at peak flexion) greater on -20° compared to 0° OG. Post-SCI, the ankle was more flexed on level surfaces compared to preSCI, and the positive relationship between decline angle and degree of ankle flexion identified preSCI was no longer present postSCI. In fact, the opposite was found with the ankle more extended on -20° compared to 0° postSCI. Tract tracing experiments are currently underway to determine if the vestibulospinal tract corresponds to the degree of yield impairments on declines as vestibular inputs facilitate adaptations to declines in uninjured animals. These findings are important clinically as the inability to adapt to declines leads to gait instability and increased energy expenditure when walking in this more challenging environment. This in turn leads to decreased community ambulation due to fear of falling and fatigue from the high cost of walking in challenging conditions. Rehabilitation must address these impairments by training gait in simple contexts such as those in the therapy gym and in more complex settings that mimic everyday situations in the community. Support contributed by: Drexel CNHP Dean's R3 grant (LRM); NIH R01 NS097880 (MRD)

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Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

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Program #/Poster #: PSTR339.11/D53

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Lonestar Paralysis Foundation gift
Neuraptive
University of Texas POC Grant

Title: Polyethylene-glycol (PEG-fusion) Technology to Treat Traumatic Spinal Cord Injuries

Authors: *A. OLIVAREZ, L. ZHOU, A. M. SCHAFER, A. AGARWAL, G. D. BITTNER; Inst. for Neurosci., Univ. of Texas at Austin, Austin, TX

Abstract: Most spinal cord injuries (SCIs) in mammals result in the permanent loss of many motor and sensory functions caudal to the lesion because severed spinal (CNS) axons do not naturally regenerate by outgrowth. Furthermore, Wallerian degeneration of severed distal axons rostral and caudal to the lesion often limits the ability of current repair strategies to improve functional outcomes after SCIs. However, our recent studies suggest that a novel technology to repair peripheral nerve injuries (PNIs) using a plasmalemmal fusogen, polyethylene glycol (PEG) at 3.35kD, may be applicable to repair SCIs. PEG-fusion subsequent to transection/ablation of PNIs non-selectively connects proximal and distal stumps of many severed axons, prevents many axons from undergoing Wallerian degeneration, and greatly improves voluntary behavioral recovery within 2-6 weeks. That is, our PEG-fusion technology rapidly (within minutes) and non-specifically fuses/joins cut, open axonal ends that are closely apposed, re-establishing axonal continuity across the lesion site regardless of axon diameter or modality. Therefore, we hypothesized that our PEG-fusion technology might also rapidly and randomly repair spinal long-tract CNS axons following SCIs. Our preliminary data demonstrate that PEG-fusion immediately restores compound action potentials recorded epidurally following various types of dorsal hemisection SCIs. Rats with spinal axons repaired by PEG-fusion exhibit better behavioral recovery compared to Negative Controls not treated with PEG following various spinal transections at T8. We also explore whether the PEG-fusion repair improves SCIs using an ablation injury model. A spinal cord segment at T9 is removed by micro-suction and replaced with viable peripheral nerve allografts (VPNAs) that span the injury. PEG is applied to the injury site to fuse the closely apposed VPNAs and spinal axons. Our preliminary data suggest that PEG-fusion has some immunoprotective effects on VPNAs as assessed by (1) reduced adaptive immune cell infiltration, (2) maintenance of the graft structure, and (3) preservation of many myelinated axons compared to Negative Controls that have transplanted VPNAs without PEG. Together, these findings suggest that the PEG-fusion technology could become a promising treatment for traumatic SCIs, as it has for PNIs.

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Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: NSERC CGSM (2023-2024)
Ontario Graduate Scholarship (2022-2023)
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MITACS
SONA/Vee Technologies

Title: Individualization of a myoelectric classification system to optimize information transfer after spinal cord injury

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Abstract: **Rational and Objectives:** Impairment in upper limb function after cervical spinal cord injury (SCI) can substantially reduce independence and quality of life. Sophisticated assistive technologies exist to restore grasping function, such as exoskeletons or functional electrical stimulation systems, but require high-bandwidth information transfer between the user and device. While myoelectric control algorithms can be used, they rarely account for the varying muscle impairment patterns characteristic of SCI. By modifying the number of gestures recognized (GN) and the rate of change of gestures (GR) to values appropriate for a given user's impairment, we aim to optimize the information transfer rate (ITR) on an individual basis. The objectives are to: 1) demonstrate that optimization of system parameters (GN and GR) for a user with SCI can increase the ITR; and 2) characterize the relationship between optimal design parameters and pattern of impairment.
Methods: 14 participants, 10 uninjured and 4 with cervical SCI, were recruited. 8 surface electromyography (sEMG) channels were placed on the forearm via anatomical landmarks. A tracing task along with manual muscle testing (MMT) scores from the muscles where electrodes were placed were used to characterize level of volitional control and pattern of motor impairment. Participants performed a series of trials varying GN (2 - 10) and GR (5, 10, 15) for a gesture classification system. ITR was computed for each combination based on GN, GR, and the achieved classification accuracy.
Results: Preliminary results show all SCI participants have peak ITR at non-maximal conditions of GN and GR, unlike uninjured participants. This was most observed with variation in GN, as GR did not significantly affect classification accuracies. For participants with SCI, the improvement in ITR between the optimal parameter choice for each user and parameter choices fixed *a priori* was 40.5 +/- 35.2 %. The large variability was due to the diversity of impairment across participants, with less impaired individuals benefiting less from the optimized parameters. A moderate correlation was observed between GN and averaged MMT score or mean squared error (r=-0.494 or 0.510, respectively), across all tested subjects. No significant correlation was found for GR with any of the assessment parameters.
Conclusions and Significance: Optimizing the myoelectric classification system based on the

user's pattern of impairment can increase ITR and improve assistive technologies for users with SCI. With more participants, a model predicting optimal GN and GR for a given impairment pattern will be created.

Disclosures: J.M.I. Eby: None. **J. Zariffa:** None.

Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR339.13/D55

Topic: C.11. Spinal Cord Injury and Plasticity

Support: K99NS135194

Title: Vagus Nerve Stimulation and Its Effect on Pairing with Bladder Voiding in Rats.

Authors: *J. J. A. ADDO[1], M. SARGUSINGH[1], T. DANAPHONGSE[2], N. BODANKI[2], J. HABEEB[2], M. A. SALINAS[1], P. E. ZIMMERN[3], M. S. DAMASER[4], S. A. HAYS[1], A. G. HERNANDEZ-REYNOSO[1];
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Abstract: Spinal Cord Injury (SCI) affects approximately 300,000 people in the U.S. One of the most prevalent and problematic symptoms of incomplete SCI above the sacral region of the spinal cord is the onset of detrusor-sphincter dyssynergia (DSD). DSD arises from the disruption in neural communications between the micturition control centers in the brain, the bladder, and urinary sphincters located below the level of the spinal cord injury. This dyssynergia is characterized by bladder contractions against a non-relaxing urethral sphincter, resulting in poor voiding efficiency. This chronic urine retention induces altered bladder compliance, which in turn results in high bladder pressure and potential kidney damage. The gold standard of care is intermittent catheterization and timed voiding to prevent involuntary leakage; however, catheterization can lead to recurrent urinary tract infections. Therefore, it is no surprise that individuals with SCI rank restoration of bladder function among their top priority, thus highlighting the critical need for more effective alternative approaches to improve bladder drainage. Vagus nerve stimulation (VNS) promotes the release of neuromodulators such as acetylcholine and norepinephrine . VNS has emerged as a prominent and widely utilized approach to drive neuroplasticity and restore function after neurological injury or disease. Pairing VNS with upper limb rehabilitation after SCI has been demonstrated to enhance recovery of motor pathways in the brain and spinal cord. Here, we hypothesize that pairing VNS with bladder voiding can change the voiding output. Adult female Sprague Dawley rats were trained to tolerate a soft-cloth restraint and awake transurethral (PE-50 catheter) retrograde filling of the bladder. Bladder pressure (P_{ves}) was continuously monitored throughout 1 hour-long fast-rate

awake cystometry (12 mL/h) sessions for two weeks. VNS was delivered when either a sudden rise of P_{ves} or voiding from the opening of the urethra was observed. Slow fill awake cystometry (5 mL/h) was done at baseline and at the end of the study to quantify urodynamic metrics. Preliminary results suggest that there is an approximately 40% increase in the voided volume and a 40% decrease in maximum bladder pressure compared to baseline measurements, with no apparent change to the inter-contraction interval. This study represents the first effort to pair VNS with bladder function. Results suggest that VNS paired with bladder function is a feasible approach to modify bladder outcomes that may be translated to SCI patients to improve their urinary dysfunction.

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Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR339.14/D56

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Evaluation of transspinal stimulation on autonomic function and quality of life in subjects with spinal cord injury

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Abstract: Currently, there is no treatment available that can reverse the loss of motor, sensory, or autonomic functions following a traumatic spinal cord injury (SCI). Trans Spinal electrical stimulation (tSCS) involves applying electrical current below the level of the spinal cord injury using surface electrodes placed between the intervertebral spaces. Its use has shown benefits in movement and posture in SCI patients, and anecdotally, improvements in autonomic and sensory function have been reported in cross-sectional studies and in a small number of subjects.Also it has shown promising results in studies published in other countries, it has proven to be safe, painless, and has no reported side effects at the moment.Methodology: The session lasts about 45 to 60 minutes. Vital signs are taken, electrodes are placed on the anterior part, being the iliac crests, and on the posterior part, in the intervertebral spaces. Electrosstimulation is emitted with parameters of 30 Hz, pulse of 1ms with intensity of 10-80 mA along with 30 minutes of physical therapy. Adult subjects with SCI below C7 will be recruited, tSCS will be applied once a week for two months, however, questionnaires will be administered at the beginning and end of treatment, and tests will be conducted at one and two months to determine if the effects persist post-intervention. Results: Four of the patients presented an ASIA A lesion (complete), of these patients in the Neurogenic Bladder Screening (NBSS) after three months of evaluation there was a noticeable difference in incontinence, there was an improvement in symptoms. In the quality of

life questionnaire (QLI-SCI), the patients made a questionnaire of satisfaction with different aspects of their life and the importance they give to each thing, where 3 of the patients, after 3 months, increased satisfaction and importance in the different areas of their life. Subjectively, the patients were asked about their perception of improvement in urination, lower limb sensitivity, lower limb temperature and sexual function, in which three of them had a noticeable changes, according to their perception. Conclusion: Improvement was observed in 4 of 5 patients, in the case of one of the patients, does not had any favorable result, we speculate that the lesion time of more than 30 years prevented better results. In the case of 2 patients, autonomic function improved considerably, mainly in bladder incontinence. The improvements in autonomic function were reflected in a better quality of life. All patients decided to continue with the treatment, since they perceived improvement in their quality of life.

Disclosures: D. Pinto: None. **M. Aliseda Marin:** None.

Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR339.15/D57

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig Neilsen SCIRTS Pilot Research Grants (No. 882102)
NRF Korea Excellent Young Research Award (No. 00209864)

Title: Promoting peristalsis after spinal cord injury using electrical stimulation of the colon

Authors: J. ZHENG[1], C. G. GEOFFROY[2], A. DOUTHITT[3], P.-H. CHUNG[1], B.-J. YOON[4], ***H. PARK**[5];
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Abstract: Neurogenic bowel dysfunction, a generic term for the loss of bowel functions, is a common complication associated with spinal cord injury (SCI). However, current solutions have limited effects and are effective mostly on the descending colon. Direct electrical stimulation (E-stim) onto the colon wall has been demonstrated in multiple intact animal models as being efficient in promoting colonic functions. However, its application in the context of SCI has not been tested so far.
The objectives of this study were to 1) investigate the changes in colonic activity after SCI and 2) determine the optimal stimulation parameters promoting colonic activity. E-stim was applied to the serosal surface of the colon in mice with SCI, with two different current amplitudes (1mA or 2 mA), and an electrocolonogram was recorded simultaneously. We pre-processed the recorded signal with a wavelet denoising technique to minimize unnecessary artifacts, smoothed

the signal with the moving average technique, and obtained the envelope of the signal. To quantify the level of colonic activity, we calculated the amplitude, frequency, and duration of the meaningful events, determined by the preset threshold based on the root-mean-square (RMS) of the entire recording. We represented amplitude, frequency, and duration of the events by peak amplitude normalized to the noise level, number of neural activities per minute, and average event duration per minute, respectively.
Experimental data showed that the frequency (number of neural activities per minute) and duration (average event duration per minute) of recorded signal decreased after SCI compared to uninjured mice, while the amplitude (normalized peak amplitude) was not altered. Importantly, both frequency and duration were increased by the application of E-stim with 1mA current amplitude, while not effects were observed in the 2mA stimulated group. Amplitude did not change for any of the E-stim groups. This result demonstrates that spinal cord injury decreases colonic activity and E-stim increases colonic activity if applied with proper stimulation parameters. This demonstrates that stimulation parameters should be carefully selected for E-stim to effectively increase the colonic activity after spinal cord injury and potentially promote colonic motility to address the problem of neurogenic bowel dysfunction.

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Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

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Program #/Poster #: PSTR339.16/D58

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Pennsylvania SCI

Title: Functionally Restorative Capabilities and Advantages of Virally Administered Retrograde CaRheb in a complete Spinal Cord Injury Model

Authors: *J. D. PASTORINO, V. J. TOM, S. F. GISZTER;
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Abstract: Spinal cord injury(SCI) results in some loss of sensation and motor function with no efficient cure. In order to promote spinal cord repair and motor control after injury, we look to induce neural growth from the motor cortex, provide a suitable bridge for this neuronal growth, bypass the CSPG barrier, perform exercise therapy, and restore functional hind limb activity in rats. Viral constitutively active ras homolog (caRheb) injections specifically promote neuronal growth rostral to injury and combined with chondroitinase ABC (chABC) intrathecally delivered support growth beyond a peripheral nerve graft of pro-reparative Schwann cells. Manipulating the mTOR pathway via silencing PTEN has previously induced growth but also increases in soma sizes as well as dendritic arbors resulting in various negative phenotypic outcomes

including seizing. It is hypothesized that using a less aggressive mediator of MTOR pathways will avoid those complications. Retrograde AAV (rAAVretro) delivery of caRheb may target those descending corticospinal cells and other descending neurons projecting to thoracic spinal cord without soma/dendritic hypertrophy. Activating lumbar central pattern generators (CPGs) via brain derived neurotrophic factor (BDNF) promotes stepping combined with robot rehabilitation therapy for strengthening step CPG circuitry and trunk muscle controls. After 6 weeks of robot-coupled treadmill therapy, caRheb animals appear to show more frequent body weight support stepping (n=8). Kinematic scores also indicate treadmill training and the neural bridging interact with the other therapies, avoiding a late collapse in function as often seen BDNF without bridging. Cortical cell soma sizes are not significantly different between groups, indicating that the caRheb is not inducing hypertrophy of cells. Subsequently, there are no observed seizure outcomes of caRheb-receiving rats, suggesting advantages over some other mTOR enhancers(n=16). Further, it is observed that animals receiving treadmill training combined with caRheb have overall improved long-term health outcomes and decreased attrition rates. Neural bridging growth results to date replicate results of Dr. Houle and Co-PI Dr. Tom (Spinal Cord Research Center).

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Poster

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Praxis Spinal Cord Institute Funding, G2020-34
Natural Sciences and Engineering Research Council of Canada Discovery Grant, RGPIN-2017-06790

Title: Enhanced corticospinal excitability in lower limbs following functional electrical stimulation therapy for standing balance in individuals with spinal cord injury

Authors: K. FOK[1], W. PEI[2], S. TAJALI[3], D. LIM[1], J. W. LEE[4], K. MUSSELMAN[5], ***K. MASANI**[6];
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Abstract: Functional electrical stimulation (FES) therapy is widely used for upper limb rehabilitation but less so for enhancing standing balance, with the underlying mechanisms remaining underexplored. Here we aimed to investigate the impact of FES on the neuromechanics of standing balance. Participants included sixteen able-bodied individuals and

eleven with chronic motor incomplete spinal cord injury (iSCI). They underwent two sessions of visual feedback balance training (VFBT) both with and without FES (FES+VFBT), scheduled at least 48 hours apart. Motor evoked potentials (MEP) from transcranial magnetic stimulation, targeting the soleus and tibialis anterior muscles, i.e., corticospinal excitability, and soleus F-waves, i.e., spinal excitability, were assessed before and after each session. Results indicated a significant increase in soleus MEP amplitudes following FES+VFBT compared to VFBT alone (36.1 ± 41.5% vs. 0.461 ± 26.2%, $p < 0.001$) for the combined groups. No significant changes were noted in the tibialis anterior MEP amplitudes (55.2 ± 94.3% vs. 13.1 ± 47.0%, $p = 0.077$). Specifically, in participants with iSCI, soleus F-wave amplitudes were significantly higher post-FES+VFBT compared to VFBT (48.4 ± 77.6% vs -9.69 ± 44.8%, $p = 0.003$), a trend absent in able-bodied participants (5.78 ± 51.6% vs. -3.78 ± 25.1%, $p = 0.507$). Additionally, FES did not affect body movement metrics, such as center of pressure velocity, during VFBT. In conclusion, combining VFBT with FES therapy significantly enhances corticospinal excitability of the plantarflexors in a single session. Particularly after iSCI, these modifications appear to be partially driven by increased spinal level excitability. Given the absence of differences in body movement metrics, these results highlight the importance of neuromodulation over motor learning based on advanced movements for inducing therapeutic benefits.

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Poster

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Program #/Poster #: PSTR339.18/D60

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Feinstein Institutes for Medical Research

Title: Human Avatar Control and Shared Tactile Perception Using a Bidirectional Brain-Computer Interface with Applications in Tetraplegia and Cooperative Neurorehabilitation

Authors: *E. CATER[1], S. CHANDRASEKARAN[3], A. JANGAM[3], Z. ELIAS[3], E. IBROCI[3], S. K. WANDELT[3], C. MAFFEI[5,3], D. GRIFFIN[5], S. BICKEL[4], A. B. STEIN[6], A. D. MEHTA[2], M. F. GLASSER[7], C. BOUTON[3];
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Abstract: Restoration of hand function remains a high priority for those living with tetraplegia. Bidirectional neural bypass (BNB) technology, which combines a brain-computer interface

(BCI) with neuromuscular electrical stimulation (NMES) can partially restore hand sensorimotor function for individuals with paralysis. Tactile-based object discrimination has been achieved in humans by peripheral nerve stimulation or, in limited studies, with intracortical microstimulation (ICMS) to primary somatosensory cortex (S1). Recent studies demonstrate that machine learning enables decoding of motor intention from human primary motor cortex (M1) activity. We aimed to achieve voluntary hand grasping simultaneously with tactile discrimination of three physical objects based on compliance via an implantable bidirectional neural bypass in a participant with a C5 complete SCI using a human avatar paradigm. Five microelectrode arrays were implanted in the left S1 and M1 of the participant. Force sensors were taped to the right D1 and D2 of an able-bodied avatar. An NMES electrode array was attached to the avatar's right forearm to recruit hand flexors when stimulated. The avatar NMES paradigm allowed us to evade any residual or recovered sensation in the participant's hand, as well as lower motor neuron dysfunction leading to poor grip strength. Three balls of varying density were placed into the avatar's hand in pseudorandom order in a learning phase (participant observed grasping) and discrimination phase (participant was blinded to object). In test trials, the participant initiated the avatar's grasp via real-time recurrent neural network-based M1 decoding. Force values were combined and linearly mapped to stimulation amplitude. Based on predetermined force thresholds, stimulation was delivered via 3, 5 or 9 electrodes in S1 evoking sensation in the D2 fingertip. Object discrimination accuracy during computer-controlled trials was 74.2% (89/120). In participant-driven trials, the participant grasped the object in all presentations, indicating that successful M1 decoding was achieved even with simultaneous S1 stimulation. Discrimination accuracy in decoder-driven trials was 64.3% (27/42). Our results show that simultaneous M1 decoding and S1 stimulation via BNB enable voluntary grasping and object discrimination in an SCI participant via another human's hand and can contribute to restoring vital hand function. The potential of the avatar NMES paradigm in the setting of cooperative neurorehabilitation should be explored, especially for patients with upper-limb motor deficits, such as spinal cord injury, stroke, or peripheral nerve injury.

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Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR339.19/E1

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NS104194
Craig Nielson Foundation
Philadelphia Foundation Brody Fund

Title: Impacts of epidural stimulation types on the recovery of function in combined bionic and biological SCI therapies

Authors: *A. P. BORISYUK, T. S. SMITH, K. J. DOUGHERTY, S. F. GISZTER;
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Abstract: Previously, sustained expression of brain-derived neurotrophic factor (BDNF) during SCI therapy spontaneously induced stepping in rats, however, the increasing prevalence of hyperreflexia after 3-4 weeks caused functionally deleterious 'collapse' in locomotion. To investigate this outcome and further improve BDNF-based rehabilitation, we explored combined rehabilitations using gene therapy (AAV5-BDNF), different epidural stimulation types (ES), and robotic training for SCI in rats. Interneuronal circuits in the spinal cord which provide drives to motoneurons may be organized for modular muscle control and play roles in these outcomes. Electromyogram (EMG) recordings reflect the premotor network drives. Accordingly, we employed Independent Components Analysis (ICA) to uncover modular changes in synergies. We tested if types of ES therapy can better recover and maintain locomotion by preventing BDNF-associated hyperreflexia in the combined therapy. We hypothesized that the spatial synergies underlying motor modularity would be retained after SCI and different rehabilitation outcomes but that BDNF+ES treatment would selectively target the spinal central pattern generators, resulting in different utilization of these synergies, improving locomotion. Our data show that suprathreshold ES extends the therapeutic window of BDNF-induced plasticity to significantly improve assisted locomotion before any BDNF-driven 'collapse'. ICA of EMGs revealed high post-SCI correlation values of the weighting matrices and synergy matching in all groups, supporting a conserved modular control of locomotion after SCI, even in collapse patterns. Altogether, the data suggest spatial synergies are conserved after complete SCI and combination therapy rehabilitation, regardless of collapse outcome, and that overexpression of BDNF needs to be tightly regulated in time.

Disclosures: A.P. Borisyuk: None. **T.S. Smith:** None. **K.J. Dougherty:** None. **S.F. Giszter:** None.

Poster

PSTR339: Spinal Cord Injury: Training, Rehabilitation, and Repair

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR339.20/E2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: T32 NIH NINDS Fellowship

Title: Unraveling the Role of Serotonergic 5-HTr6+ Interneurons in Sensorimotor Recovery Post-Spinal Cord Injury

Authors: *A. M. MARTINEZ;
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Abstract: Spinal cord injury (SCI) poses significant challenges to the affected individuals, with lasting functional deficits and limited treatment options. Rehabilitation has emerged as the primary approach for inducing recovery post-SCI, yet the underlying mechanisms remain poorly understood. This project seeks to elucidate the role of the serotonergic system, specifically focusing on 5-HTr6+ interneurons (INs), in sensorimotor recovery following SCI. Specific Aim 1 investigates the remapping of presynaptic 5-HTr6+ IN circuitry in response to SCI and rehabilitation. Using mouse genetics and rehabilitative treadmill training, alterations in synaptic connectivity and circuitry of dorsal horn circuits will be examined. High-resolution histological analysis will reveal changes in the integration of serotonergic and sensory inputs onto 5-HTr6+ INs post-SCI and rehabilitation, shedding light on potential therapeutic targets. Specific Aim 2 explores the impact of 5-HTr6+ IN activity on rehabilitation-based recovery. By modulating the activation of these INs during rehabilitation using inhibitory and excitatory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), functional locomotor recovery will be assessed. Computer vision and machine learning models will analyze biomechanics, while qualitative reasoning will interpret observed spinal plasticity and its effect on behavior. Successful completion of this project will unveil the critical role of 5-HTr6+ INs at the sensory-motor interface in post-SCI recovery. These findings hold promise for the development of more targeted and effective rehabilitative strategies, maximizing recovery outcomes for individuals with SCI. By elucidating the mechanisms underlying rehabilitation-based recovery, this research contributes to the advancement of translational treatments, offering hope to those affected by SCI.

Disclosures: A.M. Martinez: None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.01/E3

Topic: D.02. Somatosensation – Touch

Support: Swiss National Science Foundation TMAG-3_209271
Swiss National Science Foundation 310030_219343

Title: Context representation in mouse frontal cortex during a short-term memory task

Authors: P. GHADERI, S. CROCHET, ***C. PETERSEN**;
Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland

Abstract: Flexible integration of sensory information in a context-dependent manner is a key cognitive process required to generate appropriate behavior. An intriguing question, then, is how the same sensory stimulus can be interpreted differently according to context in order to generate different behavioral responses. We designed a task in which thirsty head-restrained mice were trained to lick for a water reward in response to a brief single whisker stimulus if it was preceded by a brief Go-tone presented one second before the whisker stimulus, but not if it was preceded by a NoGo-tone. Optogenetic inactivation of primary whisker somatosensory cortex (wS1), secondary whisker somatosensory cortex (wS2), secondary whisker motor cortex (wM2), or anterior lateral motor cortex (ALM) during the presentation of the whisker stimulus strongly decreased the probability of licking in the reward window in Go-trials. Inactivation of wM2 and ALM during the delay between the Go-tone and the whisker stimulus also strongly reduced licking in the reward window. We recorded neuronal activity in auditory cortex (A1), wS1, wS2, wM2 and ALM using multiple Neuropixels probes simultaneously. Prominent persistent activity following the Go-tone presentation was found selectively in wM2 and ALM, even in trials devoid of delay period movements. Using linear decoding of neuronal activity, we found that the accuracy of classifying context in the 200 ms before the whisker stimulus was significantly higher than the baseline chance level, with the highest accuracy in wM2 and ALM. Temporal correlation analysis showed that the contextual information was maintained in frontal areas through stable persistent activity. Consistently, it was possible to classify context with high accuracy from the neuronal activity of wM2 and ALM, throughout the delay period, using a classifier trained only on the last 200 ms of the delay period. These findings suggest a crucial role for the frontal areas wM2 and ALM in the encoding and maintenance of contextual information in a short-term memory task. In ongoing analyses, we aim to determine which classes of neurons in wM2 and ALM are most involved in context coding, how neurons in different cortical regions interact, and how the context-dependent delay period activity gates the transformation of whisker deflection-evoked sensory responses into licking motor initiation signals to obtain reward.

Disclosures: P. Ghaderi: None. **S. Crochet:** None. **C. Petersen:** None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.02/E4

Topic: D.02. Somatosensation – Touch

Support: Shurl and Kay Curci Foundation
RCSA #29062
NIH T32NS126122

Title: Cortical and subcortical mechanisms for tactile detection

Authors: A. Y. NAM[1], J. SHIN[2,1], M. TENNEY[1], B. ZHANG[4,1], *K. HONG[3];
[1]Biol. Sci., [3]Biol. Sci. and Neurosci. Inst., [2]Carnegie Mellon Univ., Pittsburgh, PA; [4]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The role of the cerebral cortex in detecting stimuli is controversial. While most studies take a cortical-centric view on sensory processing, numerous subcortical areas also receive bottom-up sensory inputs to mediate sensory-guided behaviors. What does the cortex contribute to evolutionarily ancient subcortical structures? Previous work indicated that acute inactivation of primary somatosensory cortex (S1) partially impairs tactile detection behavior. However, when S1 is permanently ablated, detection is only transiently impaired, rapidly recovering to pre-lesion levels within days. In the absence of S1, the midbrain superior colliculus (SC) is thought to mediate tactile detection, but its functional contribution in the intact animal remains unclear; plasticity in SC may modify its role to compensate for the loss of S1 activity, or SC may be redundant for simple tactile detection. Here, we investigate the contributions of S1 and SC in mice performing a whisker-mediated tactile detection task. Using animal behavior, optogenetics, and simultaneous S1 and SC in vivo array recordings, our results suggest that S1 and SC carry redundant information about the presence of a tactile stimulus, and that S1 activity modulates SC activity during perceptual decision-making. Potential mechanisms of coordinated S1 and SC activity for tactile decision-making are discussed.

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Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.03/E5

Topic: D.02. Somatosensation – Touch

Support: R01MH085074

Title: Mechanisms determining the degree of balance between excitatory and inhibitory activity in the neocortex during idling and evoked state

Authors: *Z. ZHOU[1], F. R. FERNANDEZ[2], B. DEPASQUALE[1], X. HAN[1], J. A. WHITE[1];
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Abstract: In neocortex, the idling state during quiet wakefulness is characterized by activity that is highly variable. Sensory activation reduces this variability. Among a number of computational models that have been advanced to support this result, our previous single-cell data are most consistent with those in which inhibition is recruited supra-linearly during increased network activation, stabilizing the network response and reducing network variability. To study this problem at the network level, we performed two-photon calcium imaging in layer 2/3 of somatosensory cortex in Parvalbumin (PV)-Cre transgenic mice (n=6) expressing AAV-syn-

jGCaMP8f and pAAV-FLEX-tdTomato. During imaging sessions, we activated the somatosensory cortex of each mouse by applying multiple air puffs of different strengths (10 psi, 30 psi) directed at their whiskers contralateral to the imaging hemisphere. In the idling state, cortical activities are balanced by sparse, asynchronous excitatory and inhibitory activities. Under the presence of strong air puffs, activity correlation increases within and between excitatory and inhibitory neurons. Upon the presence of the first air puff, inhibitory PV neurons show an average estimated firing rate that is 54% higher than that of excitatory cells. PV neurons show greater increase in firing rate than excitatory neurons. We also observe that both cell types adapt to stimulation and their firing rates decrease as more air puffs are delivered to the whiskers. Consistent with our prior results, these data support inhibition-stabilized models. To measure firing rate more accurately and to assess correlation at faster time scales, we are also obtaining membrane voltage measurements from neuronal populations in-vivo using the targeted illumination confocal (TICO) microscope. PV-Cre mice (expected n=8) are injected with AAV-syn-Voltron2 and AAV pCAG-FLEX-EGFP. Similar air puff stimulations will be delivered during imaging sessions. The TICO microscope has advantages such as kilohertz frame rate, wide imaging FOVs, and is less technically challenging than in-vivo patch-clamp recordings. With the ability to capture spiking activities and subthreshold voltage fluctuations in multiple neurons simultaneously, we are able to further validate the theories behind inhibition-stabilized models. The novel wide field subthreshold voltage data complement the calcium imaging data and support the construction of a more robust, physiologically accurate cortical network model, which will provide a more well-rounded theoretical framework for future experimental and computational work.

Disclosures: Z. Zhou: None. **F.R. Fernandez:** None. **B. DePasquale:** None. **X. Han:** None. **J.A. White:** None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

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Program #/Poster #: PSTR340.04/E6

Topic: D.02. Somatosensation – Touch

Support: DFG STA 431/14-1

Title: Consequences of individual PV and VIP interneuron firing on the output of postsynaptic SST neurons in mouse barrel cortex

Authors: F. PREUSS, M. MOECK, M. WITTE, *J. STAIGER;
Dept. of Neuroanatomy, Univ. Med. Ctr. Goettingen, Goettingen, Germany

Abstract: In recent years, the disinhibitory circuitry of the rodent neocortex has been an extensive field of study. Somatostatin- (SST) expressing cells are known as powerful inhibitors of excitatory pyramidal cells. Parvalbumin- (PV) and vasoactive intestinal polypeptide- (VIP)

expressing cells have been shown to inhibit SST cells, resulting in an expected reduction of inhibitory modulation of excitatory cells. Subcellular distribution of PV synapses (probably being perisomatic) and VIP synapses (probably being dendritic) suggests differences in their modulation of action potential generation in postsynaptic SST cells. To test this hypothesis with paired recordings, we induced action potential firing in postsynaptic SST cells to analyse the effect of simultaneous presynaptic firing of individual PV and VIP cells on SST cell spiking activity. Both cell types were able to significantly decrease action potential numbers in postsynaptic SST cells. However, there was no significant difference in spike loss of PV to SST versus VIP to SST connections. Notably, VIP cell effect strength on SST cell spiking normalised for the number of presynaptic action potentials was significantly larger than that of PV cells. Within both connections, there was a large variability in effect strength. Short presynaptic stimulation of PV and VIP cells applied before SST cell firing was able to significantly delay firing in SST cells. Again, effects were not significantly different between both groups. Also precise short firing tested at multiple positions in the evoked train of SST cell activity did not reveal significantly different effect strengths between both groups. In line, morphological analysis of putative contact sites (PCS) did not reveal differences in PCS location of VIP and PV boutons. We propose that individual GABAergic neurons are indeed able to modulate the firing output of SST neurons without principle cell type specificity. Thereby, these findings challenge the concept of a strict separation of input versus output control by different types of inhibitory cells and warrant more refined studies to assess the effect of specific disinhibitory connections on small neuronal network activity.

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Poster

PSTR340: Barrel Cortex

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Program #/Poster #: PSTR340.05/E7

Topic: D.02. Somatosensation – Touch

Support: NIH Grant 2 R01 NS092367
NIH Grant 5 K99 NS129753-02

Title: Attentional capture by reward history in whisker somatosensory cortex

Authors: *D. L. RAMAMURTHY, L. RODRIGUEZ, C. CEN, S. LI, A. CHEN, D. E. FELDMAN;
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Abstract: History-based biases allow animals to identify and exploit statistical regularities in a complex and ever-changing natural environment by using prior information to guide adaptive behavior. In humans, prior reward serves as a powerful cue for capturing attention - sensory stimuli that were recently rewarded show enhanced sensory processing, even in situations where

they are no longer important for current goals. The neurobiological mechanisms underlying this form of attention are not clear. Genetic tools in mice are powerful for identifying precise neural circuit mechanisms underlying different forms of attention. Using a novel whisker touch detection task, we have demonstrated that mice use the recent history of stimulus-reward association to dynamically modulate sensory processing of spatially specific whisker stimuli on a rapid trial-by-trial timescale, consistent with the hallmark effects of attentional selection. These effects exhibited a distinct somatotopic gradient, suggesting a neurobiological substrate in an early sensory area like primary somatosensory cortex (S1). Two-photon calcium imaging and high-density single-unit recordings in behaving mice revealed that a major fraction of S1 neurons show robust history-based cueing of sensory-evoked responses. History cueing boosted L2/3 pyramidal cell activity, shifting receptive fields of neurons towards the attended whisker. Attentional modulation was somatotopically structured and localized to a few barrel columns within the S1 whisker map, centered on the attended whisker column. Single trial decoding of neural population activity indicates enhanced stimulus information in S1 for history-cued stimuli and predicts spatially specific enhancement of behavioral detection. By contrast, L2/3 VIP interneurons were broadly activated by sensory stimuli, motion and arousal, with only a small subpopulation of these cells showing activity boosted by history cueing to the columnar whisker. These results together with spike recording results that show history cueing effects in L4 argue against L2/3 disinhibition as a mechanism for this form of attention. This work demonstrates the strong influence of non-sensory, cognitive signals in sensory cortex and establishes a new experimental paradigm to interrogate cell type-specific mechanisms underlying flexible control of behavior.

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Poster

PSTR340: Barrel Cortex

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.06/E8

Topic: D.02. Somatosensation – Touch

Support: R01NS107383

Title: Interneuron Functional Deficiency and Negative BOLD fMRI Response

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Abstract: The functional deficiency of the inhibitory system often emerges during development and may progress to psychiatric disorders or epilepsy later in life. Interneurons, which serve as

the primary source of GABAergic inhibition in the cerebral cortex, establish direct connections with arterioles and play a role in regulating vasomotion. This study aimed to replicate the functional deficiency of interneurons by employing localized microinjections of the GABA antagonist, picrotoxin, at a concentration that does not induce epileptiform neuronal activity. We conducted a series of experiments: first, recording the dynamics of resting-state neuronal activity following picrotoxin injections in the somatosensory cortex of awake rabbits; second, assessing the altered neuronal and hemodynamic responses to whisker stimulation using BOLD fMRI and electrophysiology recordings; and third, evaluating brain tissue oxygen levels before and after picrotoxin injection. Our findings revealed an increase in neuronal activity following picrotoxin administration, accompanied by negative BOLD responses to stimulation. Vasoconstriction during the resting baseline was not observed. These results suggest that picrotoxin induced imbalanced hemodynamics, possibly due to heightened neuronal activity, diminished vascular response, or a combination of both.

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Poster

PSTR340: Barrel Cortex

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Program #/Poster #: PSTR340.07/E9

Topic: D.02. Somatosensation – Touch

Support: NIH-NINDS 1K08NS114165-01A1
American Academy of Neurology Neuroscience Research Training Scholarship 2199

Title: Parvalbumin interneurons regulate circuit plasticity in the healthy and injured somatosensory cortex

Authors: B. CAMPOS[1], B. VASQUEZ[1], ***W. ZEIGER**[2,3];
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Abstract: Circuit remapping occurs during development, learning, and in response to sensory experience. This capacity for plasticity might also offer an avenue for recovery after an injury to the brain. For example, it has been widely hypothesized that plasticity and remapping of circuits underlies recovery after stroke. However, how specific changes in neuronal circuits mediate improvement in function and recovery after stroke remains a major gap in our understanding. Using a mouse model of focal cortical stroke, we previously performed longitudinal two-photon calcium imaging (2PCI) of neurons in the peri-infarct somatosensory cortex (S1). We found that sensory-evoked activity was reduced for a prolonged period after stroke and that spontaneous remapping was absent. We also found that whisker trimming-induced circuit remapping, a well-

established paradigm for experience-dependent plasticity in the healthy somatosensory cortex, was impaired. These results suggest that plasticity in the peri-infarct cortex may be maladaptive and limit recovery. We are now exploring potential mechanisms of this maladaptive plasticity by studying the role of Parvalbumin (PV) inhibitory interneurons in the healthy and injured cortex. PV cells play important roles in regulating the spatial and temporal encoding of sensory information in the cortex, and their activity has been hypothesized to gate critical periods of plasticity. Here, we used longitudinal 2PCI to record the activity of individual PV cells in the healthy S1 before, during, and after inducing experience-dependent plasticity by whisker trimming. We find that the spatial distribution of sensory-evoked responses in PV cells mirrors that of pyramidal cells. Whisker trimming leads to recruitment of PV cells responsive to the spared whisker in deprived cortical barrels, and there are long-lasting shifts in responsivity to the spared whisker in the spared barrel even after whisker regrowth. Furthermore, chemogenetic inhibition of PV cells during experience-dependent plasticity blocks whisker trimming-induced remapping. In the peri-infarct cortex, sensory-evoked responses to the principal whisker of the infarcted barrel are selectively impaired after stroke, similar to the effects observed in pyramidal cells. Together, these results suggest that proper functioning of PV cells is essential for adaptive plasticity in the healthy and injured cortex. Understanding the details of how cortical circuits change after injury will be essential for designing pharmacologic and neuromodulatory approaches to promote functional remapping and improve recovery from brain injury in the future.

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Poster

PSTR340: Barrel Cortex

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Topic: D.02. Somatosensation – Touch

Support: NIH Grant R01-NS117636
APS SURF
Michigan State Starup

Title: A morphologically distinct subclass of somatostatin-expressing interneurons in the somatosensory cortex are strongly recruited by input from the motor cortex

Authors: *M. K. SEBEK[1], G. R. GILLIE[2], D. M. AUTIO[1], M. L. RATZ-MITCHEM[1], V. SOLT[1], E. LE[1], L. E. MARTINETTI[1], K. E. BONEKAMP[3], S. R. CRANDALL[3];
[2]Neurosci., [3]Physiol., [1]Michigan State Univ., East Lansing, MI

Abstract: The motor cortex (M1) and somatosensory cortex (S1) are strongly interconnected regions, and their interactions are essential for sensory perception and motor execution. However, the mechanisms by which M1 activity modulates sensory processing within S1 are

poorly understood. In particular, M1 recruitment of distinct GABAergic inhibitory cells could impact S1 responsiveness. Preliminary work in our lab identified a subpopulation of somatostatin (SOM) expressing inhibitory interneurons in layer 6 (L6) of S1 that are strongly recruited by M1 input. We hypothesize these M1-responding L6 SOM cells are an electrophysiological and morphologically distinct subclass that express the enzyme neuronal nitric oxide synthase (nNOS). To stimulate the M1 to S1 pathway and test this hypothesis, we injected adeno-associated virus (AAV) encoding the light-sensitive cation channel, channelrhodopsin-2 (ChR2), in M1 of postnatal day 21 (+/-1) mice in vivo. After three weeks of expression, we prepared acute coronal brain slices for targeted loose-patch recordings and selective optical stimulation of M1 terminals. We found two groups of L6 SOM cells based on their spiking behavior during photostimulation: responsive (15%) and non-responsive (85%). Whole-cell recordings and neurobiotin injections into responsive and non-responsive SOM cells revealed robust electrophysiological and morphological differences. Initial anatomical reconstructions indicate that the non-responsive SOM cells (n=12) exhibit both Martinotti (with an L1 axonal projection) and non-Martinotti (no L1 axonal projection) morphologies, whereas the responsive SOM cells had axonal arborizations projecting toward the underlying white matter (n=10). The responsive SOM cells had quasi-fast-spiking electrophysiological properties (n=10) and were negative for nNOS (n=9), whereas the non-responsive SOM cells exhibited non-adaptive spiking behavior. Importantly, responsive SOM cells were negative for parvalbumin (PV), a marker for a distinct class of fast-spiking interneurons in the cortex, indicating these cells were not mislabeled PV cells due to the known off-target recombination in the SOM-IRES-Cre mouse line (n=4). The greater responsiveness of these SOM interneurons was not due to unique intrinsic properties but was produced by synaptic mechanisms. In summary, our data show that input from M1 strongly recruits a previously unknown SOM-expressing interneuron in lower L6 with distinct morphological and electrophysiological features that could influence sensory responsiveness in S1.

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Poster

PSTR340: Barrel Cortex

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.09/E11

Topic: D.02. Somatosensation – Touch

Support: AFOSR FA9550-20-1-0134
NIH R01 NS123711

Title: Label-free, activity-dependent classification of SST neuronal subtypes in superficial layers of sensory cortex

Authors: *X. MA[1], M. MOSSO[2], M. ZHU[1], A. L. BARTH[3];
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[3]Biol. Sci., Carnegie Mellon U., Pittsburgh, PA

Abstract: Somatostatin-expressing (SST) neurons are a diverse class of neocortical interneurons, characterized by at least a dozen different morphological, electrophysiological, and transcriptomic (MET) subtypes. In sensory cortex, SST neurons are densely wired into the local network and exhibit both sensory- and arousal-related activity. SST neurons in superficial layers of the primary somatosensory cortex are diverse, characterized by at least 3 major MET subtypes (defined by Chodl, Tac1/Necab1, and Calb2 expression). Because prior studies have generally combined data from all L2/3 SST neurons, it remains unknown whether these different subtypes show distinct response properties and connectivity principles in the cortical circuit. Here we used *in vivo* calcium imaging to examine the functional diversity of L2/3 SST neurons within the barrel cortex of awake mice, using multiwhisker stimulation, spontaneous activity, and locomotion/whisking-related activity to differentiate cell response properties. Using GCaMP6f expression in SST-Cre transgenic mice, we used uniformly manifold approximation and projection (UMAP) analysis to identify at least three different functional clusters of SST neurons. Using Calb2-Cre x SST-Flp transgenic mice, we found that one functional cluster mapped onto the expression of the Martinotti-linked Calb2 gene. These data suggest that label-free identification of different MET subtypes of SST neurons is possible, enabling longitudinal tracking of SST activity across different behavioral and training conditions.

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Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

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Program #/Poster #: PSTR340.10/E12

Topic: D.02. Somatosensation – Touch

Title: Large-scale neuronal dynamics underlying rapid goal-directed sensorimotor learning

Authors: *A. BISI, R. DARD, A. RENARD, S. CROCHET, C. C. H. PETERSEN;
Swiss Federal Inst. of Technol., Lausanne, Switzerland

Abstract: Animals adapt their behaviour to novel situations, quickly learning to respond appropriately to external stimuli. While different brain areas are thought to make distinct contributions to goal-directed behaviour, it remains unclear where and how new associations are formed in the brain through reward-based learning. Here, we developed a behavioral paradigm that allows us to probe rapid reward-based sensorimotor learning in mice, overcoming the limitations of longitudinal recordings. Thirsty, head-restrained mice are first pre-trained on an auditory detection task where they must lick for a reward after an auditory stimulus. Once experts in this task, these mice are transferred to a whisker-based tactile detection task, where

they must also learn to lick for a reward after a novel whisker stimulus, while continuing to perform the auditory detection task in interleaved trials. First, we observed that mice can learn the new whisker-reward association in minute timescales and go from novice to high-performance levels in a single session. Second, this learning required only a few trials to emerge and is reward-dependent, since this association was not observed in a group of mice that did not receive a reward when licking after whisker stimulation. During this single-session learning, we performed large-scale simultaneous multi-probe Neuropixels recordings across several cortical and subcortical brain areas aligned to a reference atlas. We observed widespread task-related neuronal activity across diverse areas of the brain beyond those typically considered in whisker detection tasks, including the auditory, somatosensory, motor and prefrontal cortices, dorsal striatum, and thalamus. Our experiments begin to describe the brain-wide dynamics of neuronal activity during minute-timescale learning and future work will investigate changes in inter-areal interactions.

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Poster

PSTR340: Barrel Cortex

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Topic: D.02. Somatosensation – Touch

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Title: 2-photon population voltage imaging of sensory and cognitive signal dynamics in sensory cortex

Authors: *L. C. GOMEZ[1,2], M. KIM[3], P. NALLURU[3], S. LEE[4], M. Z. LIN[5], N. JI[6], D. E. FELDMAN[7,2];
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Abstract: Neural computations in sensory cortex occur rapidly within specific subnetworks and interact with cognitive signals in ways that remain largely unclear. Studying such processes requires a method that measures the spiking dynamics of genetically identified cell types at fast timescales (5-10 ms) in large populations. Genetically encoded voltage indicators (GEVIs) offer a promising solution to overcome the slow kinetics of calcium sensors, with new GEVIs overcoming prior challenges of brightness, stability, and signal-to-noise ratio. Spatiotemporal

multiplexing of a 2photon (2p) excitation beam based on free-space angular-chirp-enhanced delay (FACED) enables deep-tissue 2p voltage imaging at kHz frame rates in large fields of view. Here, we employ a framework that combines 1) a positively tuned GEVI (ASAP4.6) with 2) both conventional small-field and FACED 2p imaging, and 3) a voltage image analysis pipeline optimized for extracting subthreshold and spiking responses from neural populations. We apply this approach to study how cognitive and sensory signals segregate and interact within functionally and genetically identified cell types in mouse whisker somatosensory cortex (S1). ASAP4.6 was expressed in layer (L) 2/3 pyramidal (PYR) cells in S1 by injection of Cre-dependent AAV in Drd3-Cre mice. Calibrated whisker deflections were delivered to awake mice engaged in a Go-NoGo auditory task while imaging voltage activity. We observed robust sensory-evoked spiking and subthreshold potentials in L2/3 PYR cells using ASAP4.6. L2/3 PYR cells tuned to different whiskers were spatially intermixed, as expected from prior calcium imaging studies. Cells tuned to columnar (CW) vs. non-columnar (non-CW) whiskers had distinct response dynamics, with CW-tuned cells having sharper tuning, shorter peak spike latency (23.0 vs 28.8 ms, p = 2e-5), and shorter PSTH response width (42 vs 48 ms, p = 4e-3). This suggests these ensembles represent distinct fast- and slow-responsive networks. We also explored the processing of unexpected stimuli that deviate from contextual regularities, suggested to be modulated by higher cortical areas. Deviant whisker stimuli in an oddball paradigm evoked long-latency subthreshold and spiking activity in PYR cells, 150-250 ms after the rapid feedforward sensory response, consistent with a top-down cognitive signal. We are currently testing whether this deviant response differs between CW and non-CW tuned subnetworks and how it may segregate in different interneuron types. These results demonstrate the power of 2p voltage imaging as a tool for investigating neural dynamics with high spatiotemporal resolution.

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Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.12/E14

Topic: D.02. Somatosensation – Touch

Support: NIH Grant U19 NS107466
NIH Grant U19 NS112959

Title: Coupling of the vibrissae to the follicle transforms touch to forces and spikes

Authors: *D. GOLOMB[1], R. LIU[2], A. FASSIHI[3], R. FARKASH[4], K. SEVERSON[5], D. H. O'CONNOR[6], D. KLEINFELD[7];
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Biol., Ben Gurion Univ. of the Negev, Be'er-Sheva, Israel; [5]Brain and Cognitive Sci., MIT, Cambridge, MA; [6]Zanvyl Krieger Mind/Brain Inst., Johns Hopkins Univ., Baltimore, MD; [7]UCSD, La Jolla, CA

Abstract: Rodents sense their surroundings by palpating their vibrissae against objects, which leads to touch-induced forces on the vibrissa shaft that are converted to neuronal signals. Torques, measured in terms of bending, are determined by the interaction between a vibrissa, the motor plant that encompasses the follicle that supports the vibrissa and the muscles that move the follicle, and an object. We observe vibrissa touch and bending during behavioral experiments in which mice "chase" and touch a moving pin. As intrinsic whisking muscles contract, the vibrissa translates mostly in a direction parallel to the skin plane, rotates toward the object, and bends upon contact. Translation and rotation are stopped by the object only for proximal objects and a large initial phase upon contact. Lastly, animals choose to make contact predominantly for distal radial object locations.
An analytical theory was developed for the limiting case of slow and small-amplitude whisking. Nonetheless, this theory provides general insights into experimentally observed vibrissa deformation upon contact. First, the peak value of the torque decreases linearly with the initial angle of contact. For distal objects, it decreases supra-linearly with the distance from the contact point to the vibrissa tip. From this perspective, the vibrissa functions like a flexible but rigidly-clamped beam for distal contacts and like a rigid body that is tightly clamped to the shaft for proximal contacts. Second, the contact duration decreases linearly with the initial phase of contact. A single missing parameter in the model, the stiffness of the mystacial, is being measured based on the analysis of contact forces that are induced by proximal objects.
All told, the contact arclength and initial phase of contact can be extracted from two observables: the contact duration and the maximal bending torque. Using these observables and known efferent copies of the vibrissa setpoint and whisking amplitude (Hill et al, Neuron 2011), the animal can in principle localize the contacted object in body centered coordinates. The transformation of torque to spikes is based on the empirical dependence of spikes on torque and d(torque)/dt (Severson et al, Neuron 2017).

Disclosures: D. Golomb: None. **R. Liu:** None. **A. Fassihi:** None. **R. Farkash:** None. **K. Severson:** None. **D.H. O'Connor:** None. **D. Kleinfeld:** None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

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Program #/Poster #: PSTR340.13/E15

Topic: D.02. Somatosensation – Touch

Support: NIH Grant U19 NS107466
NIH Grant U24 EB028942

Title: Ethological Context Toggles Spatial Encoding Strategies in Active Sensing

Authors: *R. LIU[1], P. YAO[1], D. HANSEL[2], D. GOLOMB[3], D. KLEINFELD[1];
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Abstract: Active sensing and perception serve multiple goals. This is potentially manifest as distinct streams of internal representations of external spatial information. Here we investigate whether different goals can influence the internal representation of spatial information that is acquired by the vibrissa scanning sensorimotor system. We use mice trained to whisk in two different behavior contexts, i.e., exploratory whisking and proximity detection. We conducted high-temporal and -spatial resolution measurements of the mechanics of whisking and vibrissa touch, along with high-temporal and -spatial resolution measurements of synaptic release from thalamocortical (TC) boutons in L4 of vibrissa ("barrel") cortex. During exploratory whisking the vibrissae execute protracted, rhythmic sweeps. We find that during both free whisking and touch, TC boutons predominantly encode vibrissa position in terms of phase in the whisk cycle as opposed to angle in head centered coordinates. Further, the representation of phases by TC boutons is mapped throughout the column. Conversely, in proximity detection the vibrissae execute retracted and partially arhythmic free whisking. Here we find that TC boutons predominantly encode vibrissa position by angle. Critically, some individual boutons play a conjunctive role and switch between the two encoding strategies. All told, these data indicate that behavioral context toggles thalamic encoding, and thus the perceptual content, between phase and angle representations. We are currently measuring the responses from L4 excitatory and inhibitory neurons to understand how touch is "read-out" for each of the two representations. As a general goal, this study advances our understanding of how sensory systems adapt their internal representation to meet the demands of different behavioral goals, highlighting the flexibility and context-dependency of sensory information processing.

Disclosures: R. Liu: None. **P. Yao:** None. **D. Hansel:** None. **D. Golomb:** None. **D. Kleinfeld:** None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.14/E16

Topic: D.02. Somatosensation – Touch

Support: NIH grant R35 NS127219
NIH training grant T32 GM130550

Title: Short-term synaptic depression within and between barrels in an excitatory neuron subpopulation in somatosensory cortex

Authors: *J. JUDGE[1], M. B. JACKSON[2];
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Abstract: Much of the processing of sensory inputs performed by cortical circuits is poorly understood. During typical whisking at 5-25 Hz, barrel columns in rodent barrel cortex (BC) receive excitatory thalamic input originating from hundreds of whisker deflections per second. Each barrel processes input primarily from one whisker, affording texture discrimination as sensitive as that of human fingertips. The roles of different layers in processing single-whisker deflections have received much attention, with studies in vivo revealing that a single whisker deflection depolarizes the entire barrel field in layer 2/3 (L2/3), with equally broad or even broader multi-whisker receptive fields in layer 4 (L4). Yet inter-barrel temporal processing of responses to repetitive stimulation has received less attention. In particular, the potential for inter-barrel connections to implement temporal filtering at neighboring barrels in the barrel field has not been explored. Short-term depression (STD) at glutamatergic synapses balances and limits responses to excitatory inputs, and contributes to the processing of information. This filtering may be directed to neighboring barrels based on the behaviorally-shaped input from whisking; in fact, previous studies suggest a directional bias across the barrel field created by synaptic connections. Here we used a hybrid optical voltage sensor (hVOS) to image stimulus-evoked voltage changes from many cells simultaneously in genetically-defined subpopulations in intact BC circuits. In brain slices from adult mice (8-12 weeks) of both sexes we probed pyramidal and spiny stellate cells in L4 expressing hVOS probe driven by a Cre driver (scnn1a-tg3-Cre). In this excitatory population we measured STD over interpulse intervals (IPI) from 5 to 130 ms, and tracked the kinetics of recovery. We compared STD between stimulated barrels and their neighboring barrels. We hypothesize that STD acts as a low-pass filter in synapses in the L2/3-L4 circuit, selectively transmitting low-frequency information relevant to the representation of a detected object. Uniformly sampling IPIs, we find two components of STD with distinct paired-pulse ratios, suggesting distinct mechanisms of STD within this population that contribute to temporal processing. We further hypothesize that STD may be oriented in BC to filter out whisking frequencies only from the axis along which whisking is performed, and passively attending more closely to the forward phase of the whisking cycle. We compared STD in barrels in coronal and sagittal slices and STD in rostral versus caudal neighbor barrels to test this hypothesis.

Disclosures: J. Judge: None. **M.B. Jackson:** None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.15/E17

Topic: D.02. Somatosensation – Touch

Support: NIH Grant
RO1

Title: High density neural recording from the barrel cortex reveals a spatially graded recovery following stroke

Authors: H. RATHORE[1], R. YIN[7], J. ZHANG[2], Y. JIN[3], F. HE[2], P. ZOLOTAVIN[2], C. XIE[2,4], ***L. LUAN**[5,1,6,4];
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Abstract: The brain possesses a remarkable ability to undergo spontaneous self-repair in response to injury such as an ischemic stroke. This dynamic and lasting restorative process involves a diverse array of neuroplastic mechanisms that are time and location dependent. Despite extensive research, there is still a lack of definitive evidence regarding neurons changing their functional response, leading to debates about the exact cellular mechanism of neuroplasticity. In this study, we deployed large-scale, spatially distributed electrophysiology to chronically record spike-level neural dynamics from hundreds of neurons through the various phases of a small-scale ischemic lesion. For spatially graded ischemia, we used structured illumination to create a precise photothrombotic micro-lesion on a single barrel column with fine location control. We stimulated the whisker corresponding to the stroked barrel and simultaneously recorded electrical neural activity from the peri-infarct tissue. We classified cells based on their electrophysiological signatures (regular spiking and fast spiking) and tracked the changes in neuronal populations, firing dynamics and network coupling with measurements spanning till the chronic stage after stroke. We found that stroke caused lasting neuronal damage in the near-peri-infarct region which was cell-type specific with excitatory neurons suffering the strongest neural deficit. In the regions beyond the peri-lesional tissue, far away from the infarct, our results revealed that neuronal population was robust to stroke damage. Longitudinal electrophysiology showed that a significant subset of surviving neurons enhanced their response to the stroked barrel during functional activation while other populations of neurons showed strong attenuation. This compensatory spiking activity in the far-peri-infarct was mainly found to be excitatory in nature. Finally, neurons with enhanced activity after stroke were found to exhibit strong correlation to the network activity from the rest of the population. These results suggest that neural plasticity after stroke could manifest as selective changes in the firing pattern of neurons rather than a regional shift of population response, thus highlighting the importance of direct measures of neural dynamics in studying the mechanism of stroke-induced functional reorganization.

Disclosures: H. Rathore: None. **R. Yin:** None. **J. Zhang:** None. **Y. Jin:** None. **F. He:** None. **P. Zolotavin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuralthread Inc. **C. Xie:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuralthread Inc. **L. Luan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuralthread Inc..

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.16/E18

Topic: D.02. Somatosensation – Touch

Support: NIH Grant R01-NS117636
Michigan State Startup

Title: Presynaptic inhibition of higher-order thalamocortical and corticocortical inputs to mouse somatosensory cortex

Authors: *K. E. BONEKAMP, M. L. RATZ-MITCHEM, G. GILLIE, M. SEBEK, L. XIONG, S. R. CRANDALL;
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Abstract: The strength of a given synapse is dictated by its own previous activity. Repetitive activation of synapses can change the strength of synaptic transmission, dynamically altering neuronal communication across time. In addition, other chemical messengers can contribute to the dynamic nature of synapses. For example, inhibition of presynaptic neurotransmitter release has been shown to decrease synaptic strength and short-term depression. Presynaptic inhibition is mediated by a host of neurotransmitters with receptors located on presynaptic terminals, one in particular being metabotropic gamma-aminobutyric acid (GABA) receptors, GABAB. Previous studies show that GABAB-mediated presynaptic modulation occurs at local corticocortical but not core thalamocortical synapses, suggesting potential pathway specificity to this presynaptic modulation. However, there are multiple types of thalamocortical and intracortical pathways, and it is unclear if these specificities emerge as a general phenomenon of the forebrain or if they are unique to these pathways. The mouse vibrissa system offers a well-studied, tractable model to investigate these presynaptic inhibitory effects in long-range sensorimotor communication. Various vibrissa-related thalamocortical and corticocortical pathways are essential for normal sensation, object detection, and feature discrimination. This work aims to investigate the modulation of synaptic strength in vibrissa somatosensory thalamocortical and corticocortical pathways through presynaptic inhibition. Employing *in vitro* whole-cell electrophysiological recordings with optogenetic and pharmacological manipulation, we assess how presynaptic glutamate release in layer one of the vibrissal primary somatosensory cortex (vS1) from either the vibrissal primary motor cortex (vM1) or the posterior medial nucleus of the thalamus (POm) is influenced by agonists for GABAB receptors. Preliminary work shows that applying GABAB agonists suppresses excitatory vM1 responses onto L2/3 pyramidal neurons in vS1. Our research is poised to enhance our understanding of the role of presynaptic inhibition across various types of synapses and its dynamic regulation of synaptic communication.

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Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.17/E19

Topic: D.02. Somatosensation – Touch

Support: R01NS134639

Title: Dynamics of sensory response plasticity and homeostasis following whisker deprivation in mouse S1 cortex

Authors: *L. RODRIGUEZ[1], D. FELDMAN[2];
[1]Univ. of California Berkeley, Berkeley, CA; [2]Mol. & Cell Biol. Dept., UC Berkeley, Berkeley, CA

Abstract: Neural circuits are plastic in response to experience, but also stabilize certain activity features, including mean firing rate, to stay within physiological boundaries. This balance between stability and plasticity is crucial for proper brain function. In sensory cortex, pyramidal cells (PYR) maintain their mean firing rate at a cell-specific set point, actively restoring it after sensory perturbations. This restoration involves homeostatic regulation of excitatory synaptic inputs, local inhibitory circuits, and intrinsic excitability. However, little is known about the magnitude and dynamics of homeostasis across different cortical layers. To address this, we investigated the dynamic regulation of sensory-evoked responses in whisker somatosensory cortex (S1) across days after the onset of whisker deprivation.
In prior studies in rats, depriving the D row of whiskers caused a transient homeostatic response in L2/3 of S1 (at 3 days deprivation) that stabilized or even slightly increased whisker-evoked PYR cells firing rate, followed by classical weakening of these deprived whisker responses (at 5+ days). This transient homeostasis was due to disinhibition caused by down-regulation of PV interneuron circuits, detectable at 3 days of deprivation, which masked deprivation-induced weakening of excitatory synapses onto L2/3 PYR cells. In mice, slice physiology showed that 1-day D-row deprivation is enough to reduce L2/3 PV intrinsic excitability and inhibitory output, suggesting that network homeostasis by PV disinhibition is even more rapid in mice.
Here, we studied the in vivo dynamics of homeostasis in mouse S1, in L2/3 and other layers, using Neuropixels recordings of spikes and LFP over days following onset of D-row deprivation, in anesthetized mice. By 1 day of deprivation, whisker-evoked LFP was reduced in all layers, indicating rapid synaptic weakening. Despite this, whisker-evoked spiking in L2/3 and L5 RS cells showed an early transient increase at 1 day, consistent with rapid homeostasis, followed by weakening at 3-10 days. Both early homeostasis (at 1 day) and the later transition to weakening (at 3 days) occurred more rapidly in mice than in prior rat studies. Fast-spiking (putative PV) neurons showed a strong decrease in whisker-evoked spiking at 1 day, suggesting that rapid disinhibitory homeostatic involves reduction of PV activity in both mice and rats. Spiking activity in L4 and L6 were unchanged with deprivation. Thus, weakening of PV inhibitory

circuits upon sensory deprivation quickly compensates for the loss of sensory drive in both mice and rats, which may help enhance the detection of residual sensory inputs after sensory loss.

Disclosures: L. Rodriguez: None. **D. Feldman:** None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.18/E20

Topic: D.02. Somatosensation – Touch

Title: Transient neural correlates of perceptual decision-making in primary somatosensory cortex of mice during whisker-guided locomotion

Authors: *A. G. ARMSTRONG, Y. VLASOV;
Univ. of Illinois Urbana-Champaign, Champaign, IL

Abstract: We harness the whisker-guided navigation of mice using tactile virtual reality to study ethologically relevant decision making. Head-fixed animals navigate a virtual corridor using a pair of C2 principal whiskers to track two motorized walls that are coupled to the mouse movement. This creates a baseline behavior task that relies on predictive feedback coding between sensory input and motor output. A Poisson GLM fit to neural activity of over 400 units (n=9) recorded in the principal whisker barrel (wS1) using Neuropixel probes, reveals dominant correlation to the VR feedback signal, much stronger than correlation to locomotion (speed, acceleration, gait of walking or trotting, etc.) and sensory (whiskers trajectories) variables. To study perceptual decision making induced by a non-stationary sensory input, a sudden “surprise” interrupts the baseline task as one of the walls (ipsi- or contra-lateral to the recording site) approaches the snout to emulate a virtual obstacle. To avoid collision the animal changes run direction with a mean reaction time (RT) of 250ms measured from the first whisker touch to approaching wall (stimulus onset time, SOT) to the first stride of the turn (decision onset time, DOT). Following the brief initial increase of neural activity at SOT, the activity along all the cortical layers is strongly suppressed for both ipsi- and contra-lateral turns. Following the interpretation of similar temporary dip in neural activity frequently observed in visual cortices, this transient suppression can be interpreted in terms of the reset of a decision variable (DV). While the suppression during the ipsi-lateral turns continues, the neural activity during the contra-lateral turns exhibits a strong gradual increase indicating the onset of DV integration. The activity peaks at 170ms mean time, followed by a DOT executed by an accelerated push with hind legs at RT. A diffusion-drift model (DDM) fit to RT distribution correctly predicts the suppression after sudden evidence change and the onset of evidence integration. Interestingly, the suppression and the following increase of the neural activity is delayed by almost 100ms when the wall is moving out of reach at the end of the turn trial with RT approaching 800ms. This indicates that the evidence threshold level for the DV is strongly modulated by top-down regulation. This observation is supported further with GLM decoding of specific gait from neural

data with the decoding accuracy dynamically changing over trial epochs, peaking at both DOTs. We hypothesize that these locomotion signals are embedded within wS1 activity due to predictive coding feedback loops.

Disclosures: A.G. Armstrong: None. **Y. Vlasov:** None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.19/E21

Topic: D.02. Somatosensation – Touch

Support: NINDS 5R01NS084818-09

Title: Behavior and neural basis of stimulus side discrimination in a mouse model with bilateral somatotopic maps in S1

Authors: *V. B. CHOKSHI[1], Y.-T. CHANG[2], R. S. ERZURUMLU[3], D. H. O'CONNOR[2]; [1]Johns Hopkins Univ., Baltimore, MD; [2]Zanvyl Krieger Mind/Brain Inst., Johns Hopkins Univ., Baltimore, MD; [3]Anat. and Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Mouse whisker primary somatosensory cortex (wS1), also known as barrel cortex, receives input from the contralateral whiskers due to midline crossover of the trigeminal brainstem complex projections as they project to sensory thalamus. Robo3cKO (Krox20-cre+/-;Robo3fl/fl) mice have bilateral whisker maps in wS1 due to incomplete cross over of the trigemino-thalamic projections (Renier et al 2017, Elife). We tested if having a bilateral map in wS1 disrupts their ability to correctly judge on which side of the face a single-whisker deflection stimulus was applied ("bilateral whisker discrimination task", BWD task). Surprisingly, Robo3cKO mice performed as well as wildtype (Krox20-cre-/-; Robo3fl/fl, Robo3-WT) littermates. In solving the task, do Robo3cKO mice use activity from both hemispheres, or do they "ignore" activity from the ectopic, ipsilateral whisker map? We tested this by optogenetically silencing wS1 activity in either hemisphere in a subset of the trials. We found that the BWD task performance in Robo3cKO mice depends on wS1 activity contralateral to the stimulus, as seen in the Robo3-WTs. This suggests Robo3cKO knockout mice rely on contralateral wS1 information while "ignoring" ectopic ipsilateral information.
To understand how Robo3cKO mice performed the BWD task as well as Robo3-WT mice, we used linear probe arrays to record spiking activity from single neurons in the whisker primary somatosensory cortex (wS1) and in one of its major downstream targets, the whisker primary motor cortex (wMC). We delivered a stimulus to the C2 whisker on either side of the face in lightly anesthetized mice. As expected, neurons in wS1 of Robo3-WT mice were nearly always selective for the whisker on the contralateral side. In contrast, we found that neurons in wS1 of Robo3cKO could be selective for the C2 whisker on either side with same selectivity onsets as observed in Robo3-WT mice (0-35 ms). In wMC, spiking activity in both Robo3-WT and

Robo3cKO showed contralateral selectivity early on (0-40 ms). Spiking activity of a minority of neurons in both genotypes showed ipsilateral selectivity with delayed onset (35-60 ms). Hence, unlike bilateral selectivity of spiking activity in wS1 in Robo3cKO, wMC spiking selectivity was normal and predominantly contralateral. This suggests that there exists plasticity in the wS1-> wMC pathway that allows for normal selectivity in wMC in the Robo3cKO mice.
Together, our behavioral, optogenetic and electrophysiological data indicate that the brains of Robo3cKO mice undergo functional rewiring within the whisker processing stream to facilitate normal and contralateral- dominant behavior despite a bilateral sensory cortex map.

Disclosures: V.B. Chokshi: None. **Y. Chang:** None. **R.S. Erzurumlu:** None. **D.H. O'Connor:** None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.20/E22

Topic: D.02. Somatosensation – Touch

Support: UTK URF AURA
NIH R15 (KK)
UTK Startup Fund (BL)

Title: Disruption of tactile sensory perception through cortical perineuronal net degradation in adult female mice

Authors: *J. D. MARTIN[1], K. KRISHNAN[2], B. Y. LAU[3];
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Abstract: Perineuronal nets (PNNs) are specialized extracellular matrix structures thought to restrict plasticity in the mature brain. In adult wild-type mice (WT), we found increased PNN expression in the primary somatosensory barrel field region (S1BF) after they performed pup retrieval, an ethologically relevant social behavior. This result suggests that increases in PNN expression could be important for consolidating new experiences via tactile sensation, even in the mature adult brain. In contrast, naive adult mice heterozygous for MeCP2 mutations (Het) display abnormally high PNN expression, which correlates with hyposensitivity in object recognition and texture discrimination and inefficient pup retrieval. The Het serves as an appropriate mouse model for Rett syndrome, a neuropsychiatric disorder with sensory, motor, social and cognitive phenotypes. Together, these results suggest that PNN expression needs to be tightly regulated for acquiring and consolidation of new skills and behaviors. To test this hypothesis, we injected chondroitinase ABC (ChABC) into S1BF of adult WT and Het mice to degrade PNNs and assessed their pup retrieval performance for 6 consecutive days. WT with

ChABC injected unilaterally exhibited more variable performance on the first 2 days, compared to Penicillinase-injected control WT. They subsequently improved to WT performance (n=17 animals per condition; Kruskal-Wallis test). This suggests that PNNs in the right S1BF function to acquire, rather than maintain, pup retrieval efficiency. In Het injected with ChABC bilaterally, we found no significant changes as compared to control Het injected with penicillinase (n=12; Kruskal-Wallis test). After ChABC manipulation, both WT and Het mice showed minimal tactile sensory perception responses in object recognition and texture discrimination assays. As the primary somatosensory cortex is a large region with the most PNNs in the mouse brain, we hypothesized that the variation in responses in the WT behavior could be explained by the extent of PNN degradation. Thus, we used Aligning Big Brains and Atlases (ABBA) to map and register the entire mouse brain sections to determine the regional degradation per brain. We found variable PNN degradation in multiple somatosensory subregions due to the coordinates of the injections. We are currently performing multivariate analysis and other statistical modeling to determine the specific impact of PNN reduction in individual subregions on efficient retrieval. Together, these results will determine the role of PNNs in adult primary somatosensory cortex in mouse complex maternal behaviors and simple tactile perception tasks.

Disclosures: J.D. Martin: None. **K. Krishnan:** None. **B.Y. Lau:** None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

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Program #/Poster #: PSTR340.21/E23

Topic: D.02. Somatosensation – Touch

Title: Deciphering the Regulatory Control of Neuromodulatory Signaling in the Somatosensory Cortex after Sensory Deprivation

Authors: *T. JAMAL[1], T. CELIKEL[2];
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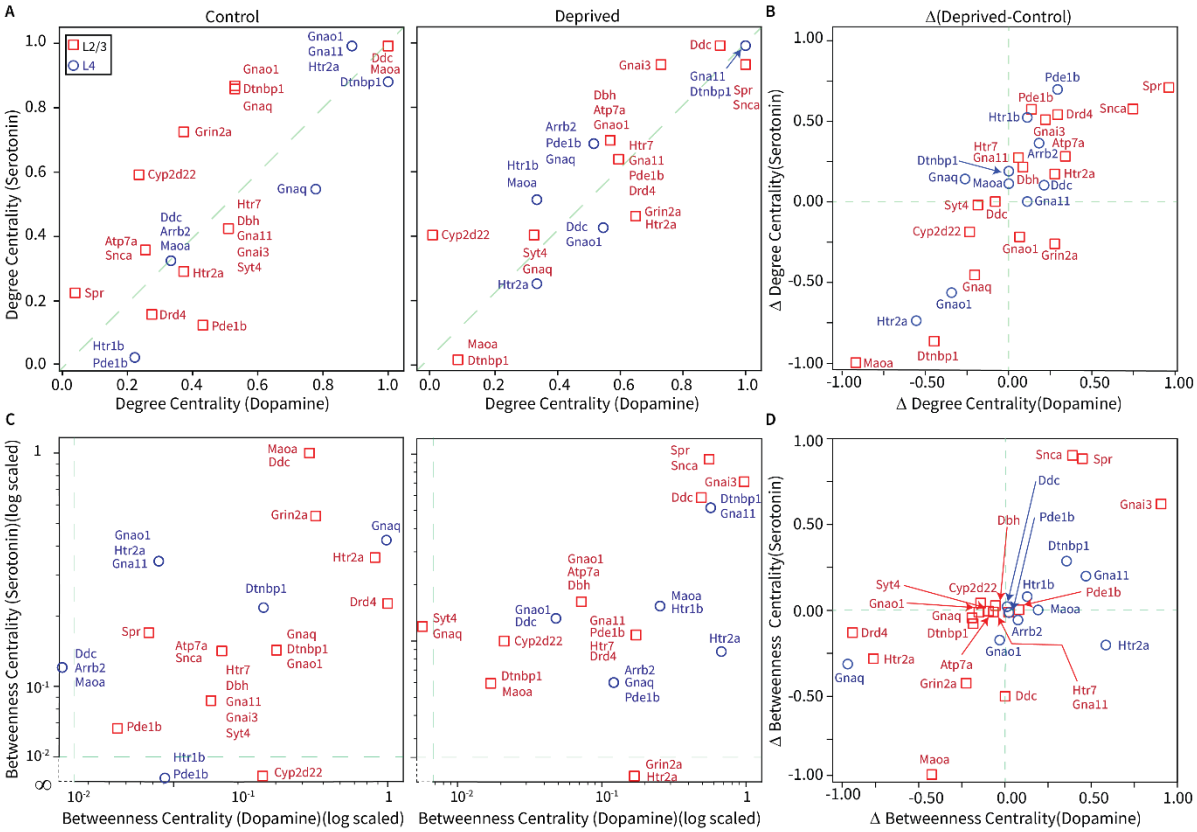
Abstract: Serotonin and dopamine are crucial neuromodulators influ- encing various aspects of brain function, including sensory processing. Recent studies have demonstrated that sensory deprivation controls gene transcription in both the dopaminergic (*DSP*) (Jamal et al, 2024) and the serotonergic signaling pathways (*SSP*) (Jamal et al, submitted) in the barrel cortex of the rodent primary somatosensory cortex (*S*1). Molecular physiological studies showed these changes might establish a close-loop regulatory control between sensory experience and neu- romodulatory signalling. These pathways are coupled systems; several nodes in the pathway contribute to various neuromodulatory processes. Here we perform a graph network analysis of the *DSP* and *SSP* using NETSCOPE (Bergman et al, 2024) to identify genes whose transcrip- tion allow common regulatory control over neuromodulatory signalling in the somatosensory cortex after whisker deprivation. Our results re- vealed that 20 transcripts are common across the

two pathways, with 8 transcripts expressed in both supragranular (layers 2-3) and granular (layer 4) layers. Centrality measures showed that transcripts common to both pathways contribute to increased coupling in layer 2/3 compared to layer 4 (see Figure 1). Interestingly, whisker deprivation resulted in increased degree centrality in both layers, indicating increased covariance in gene transcription. These sub-network formations offer a unique opportunity to regulate cortical plasticity in a targeted manner.



Disclosures: T. Jamal: None. **T. Celikel:** None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.22/E24

Topic: D.02. Somatosensation – Touch

Support: ERC Grants 633428
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German Research Foundation grant SFB 1089
German Research Foundation grant SPP 2041
German Federal Ministry of Education

Title: Broad receptive fields in cortex facilitate efficient and robust population coding of sensory information

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Abstract: In conventional views of the cortical circuitry, sensory processing starts in layer 4 (L4), where inputs from primary thalamus evoke responses in L4 neurons that are selective to specific stimulus features. However, it has become increasingly clear that in parallel to this canonical cortical circuit, the same sensory input from thalamus also drives responses in L5. In contrast to selective responses and hence narrow receptive fields in L4, L5 pyramidal tract neurons (L5PTs) respond unselectively to virtually any stimulus, and hence have broad receptive fields. We recently reported the cellular and circuit mechanisms that underlie broad receptive fields of these major cortical output neurons[1]. Based on this mechanistic insight, we now addressed the question: What stimulus information could L5PTs broadcast to downstream targets despite their broad receptive fields? We found that sensory responses of L5PTs constitute a population code that allows decoding the features of any stimulus tested. In fact, we show that sampling responses of any small subpopulation of L5PTs within and across any cortical column of barrel cortex allows for such decoding. We demonstrate that broad receptive fields and large cell-to-cell variability thereof are necessary to constitute this population code. The broader the receptive fields, and the larger the cell-to-cell variability, the fewer L5PTs are required to encode the specific stimulus features. Thus, broad receptive fields of L5PTs enable downstream targets to efficiently and robustly decode sensory information. Our findings indicate that sensory input from thalamus is transformed in parallel into two complementary population codes, one that relies on selective responses in L4, and one that relies on unselective responses of L5PTs.
1. Egger et al 2020.

Disclosures: M. Royo Cano: None. **A. Bast:** None. **R. Fruengel:** None. **C.P. De Kock:** None. **M. Oberlaender:** None.

Poster

PSTR340: Barrel Cortex

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR340.23/E25

Topic: D.02. Somatosensation – Touch

Support: This research was funded by the Max Planck Society.

Title: Roboem: automated 3d flight tracing for synaptic-resolution connectomics

Authors: *M. SCHMIDT, L. MAYER, A. MOTTA, M. SIEVERS, M. HELMSTAEDTER; Connectomics, MPI For Brain Res., Frankfurt, Germany

Abstract: Mapping neuronal networks from three-dimensional electron microscopy (3D-EM) data still poses substantial reconstruction challenges, in particular for thin axons. Currently available automated image segmentation methods require manual proofreading for many types of connectomic analysis. Here we introduce RoboEM, an artificial intelligence-based self-steering 3D 'flight' system trained to navigate along neurites using only 3D-EM data as input. Applied to 3D-EM data from mouse and human cortex, RoboEM substantially improves automated state-of-the-art segmentations and can replace manual proofreading for more complex connectomic analysis problems, yielding computational annotation cost for cortical connectomes about 400-fold lower than the cost of manual error correction. We are now exploring the usage of self-supervised techniques.

Disclosures: M. Schmidt: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application filed. **L. Mayer:** None. **A. Motta:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application filed. **M. Sievers:** None. **M. Helmstaedter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application filed.

Poster

PSTR340: Barrel Cortex

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Topic: D.02. Somatosensation – Touch

Support: ERC Grants 633428
ERC Grants 101069192
German Research Foundation grant SFB 1089
German Research Foundation grant SPP 2041
German Federal Ministry of Education

Title: Beyond the impact of morphology: Dissecting principles that constrain ion channel distributions in cortical dendrites

Authors: *S. SAKA[1], A. BAST[2], S. DURGVANSHI[2], N. C. DEMBROW[3], M. OBERLAENDER[2,1];
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Abstract: Understanding how neurons transform synaptic inputs into action potential (AP) output represents one of the key challenges for basic neuroscience research. Specifically, how synaptic input, ion channel distributions and morphology relate to one another to implement function remains generally unclear. Capturing synaptic integration along morphologically and biophysically complex dendrites via neuron models is hence essential for dissecting such relationships. However, so far, such models remain often limited to the morphology of a single neuron, or fail to reproduce physiological responses observed empirically. Here, we generate millions of such biophysically detailed models for layer 5 pyramidal tract neurons (L5PTs) that capture physiological responses as observed via dual somatic and dendritic recordings from *ex vivo* slices for a diverse set of *in vivo* labelled dendritic morphologies. We find highly disparate ion channel distributions that can account equally well for a wide range of dendritic and perisomatic responses that are observed in L5PTs *ex vivo* and *in vivo.* Why do L5PTs have such an enormous degree of freedom to implement their function? Analyzing relationships that characterize this degeneracy in ion channel distributions, we observe different principles for the ways by which L5PTs can generate calcium action potential (Ca AP) in their dendrites to facilitate somatic burst firing. These principles make predictions regarding the energy demand of Ca AP generation, as well as for the spatiotemporal organization of synaptic input patterns that are necessary to account for *in vivo* responses. Moreover, they are robust across variations in morphology and physiological responses that we used to generate the models. Thus, we reveal principles that underlie degeneracy in ion channel distributions beyond the impact of morpho-electric variations from cell-to-cell. Our database of L5PT models sets the stage to explore how synaptic input, ion channel distributions and morphology relate to one another to implement function, and how additional principles such as energy demand of active dendritic mechanisms could impact these relationships.

Disclosures: S. Saka: None. **A. Bast:** None. **S. Durgvanshi:** None. **N.C. Dembrow:** None. **M. Oberlaender:** None.

Poster

PSTR340: Barrel Cortex

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Topic: D.02. Somatosensation – Touch

Support: German Research Foundation (grants SFB 1089 and SPP 2041)

Title: Depth-dependent variations in morphoelectric properties reveal the molecular identity of cortical interneurons

Authors: *F. YÁÑEZ[1], L. MESSORE[1], G. QI[2], D. FELDMEYER[2], B. SAKMANN[3], M. OBERLAENDER[1];
[1]MPI for Neurobiol. of Behav., Bonn, Germany; [2]Inst. of Neurosci. and Med., Res. Ctr. Jülich, Jülich, Germany; [3]MPI for Biol. Intell., Martinsried, Germany

Abstract: Cortical interneurons are characterized by a variety of cellular attributes that enable their specialized roles in regulating information processing in the brain. Molecular identity provides the major subtype specification, with striking differences in morphology and electrophysiology across layers. However, it is unknown whether such diverse morphoelectric properties systematically relate to molecular identity to organize the structure underlying cortical circuits. Here we assess variations in morphoelectric properties across the entire depth of rat barrel and mouse visual cortices. These variations define relationships that reveal the molecular identity of interneurons based on their respective morphoelectric properties. In both species, the overall axonal and dendritic arborizations increase as a function of cortical depth. The spike-frequency also increases with cortical depth, whereas the spike-frequency adaptation remains unaffected by it. Interneurons with high spike-frequency and low spike-frequency adaptation z-scores delineate the parvalbumin class, including small to large basket, chandelier, and translaminar cells. This relationship is conserved across layers. Strong correspondences between morphoelectric properties and molecular identity are also observed in the remaining major interneuron subtypes. Thus, simple organizing principles may largely account for the diversity of interneurons through the adjustment of their morphoelectric properties in cortex.

Disclosures: F. Yáñez: None. **L. Messore:** None. **G. Qi:** None. **D. Feldmeyer:** None. **B. Sakmann:** None. **M. Oberlaender:** None.

Poster

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Topic: D.02. Somatosensation – Touch

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ERC grant 101069192
German Research Foundation grant SFB 1089
German Research Foundation grant SPP 2041
German Federal Ministry of Education

Title: Predicting Structure-Function Relationships in Cortex via Artificial Neural Networks

Authors: *M. R. KEATON, M. OBERLAENDER;
In Silico Brain Sci., Max Planck Inst. for Neurobio. of Behavior, Bonn, Germany

Abstract: The coupling of information streams is a hallmark feature of cortical function, and it is believed that network architecture is key to this. Neuroanatomical studies have shown that the specificity of projections of particular cell types both to and from the cortex facilitate the formation of characterizable networks. However, determining the impact these structures have on how incoming information streams are coupled and processed is not well understood and remains challenging to study. Here, we propose a computational approach to investigating this

by informing artificial neural network models with increasing detail from neuroanatomical reconstructions of the cortex. We demonstrate that by training such cortically-inspired networks on a battery of machine learning tasks, we obtain concrete predictions on how network architecture and wiring specificity therein could facilitate function. We explore such structure-function relationships with respect to biologically-relevant tasks like generalization and show how these networks compare to other possible architectures. Our approach provides promising results and empirically testable predictions which we hope will shed new light on how interareal connectivity patterns facilitate the manner by which information streams are coupled.

Disclosures: M.R. Keaton: None. **M. Oberlaender:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

Location: MCP Hall A

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Program #/Poster #: PSTR341.01/E29

Topic: D.03. The Chemical Senses

Support: The research reported here was supported, in part, by the National Science Foundation under grant #2024607

Title: Divisive normalization processing underlies odorant mixture representation in the mushroom body calyx

Authors: A. A. LAZAR[1], T. LIU[1], C.-H. YEH[1], ***Y. ZHOU**[2];
[1]Dept. of Electrical Engin., Columbia Univ., New York, NY; [2]Dept. of Computer and Information Sci., Fordham Univ., New York, NY

Abstract: The main purpose of the insect olfactory system is to find the world of odorants intelligible. Fruit flies associate meaning to odorants through associative learning. The encoding and associative learning of pure odorants have been widely studied in this model organism. However, insects live in a complex environment with odorant mixtures changing in space and time. How odorant mixtures are encoded and processed end-to-end is a major challenge in experimental/computational neuroscience.
We devise an Odorant Encoding Machine (OEM) modeling the first three stages of the early olfactory system (EOS) of the fruit fly brain leading to associative learning: the Antenna (ANT), the Antennal Lobe (AL) and the Mushroom Body Calyx (Calyx). The OEM extends our previous model of the odorant space by characterizing the space of odorant mixtures and their interaction with the Olfactory Sensory Neurons (OSNs) in the Antenna. The three processing stages of the OEM are each modeled by a Divisive Normalization Processor (DNP). Consequently, the end-to-end OEM consists of cascaded DNPs, analogous to the cascaded DNPs advanced in a model of motion detection in the early visual system [1].
We empirically evaluated the OEM on representing both individual odorants and their mixtures at the output of the Calyx, which exhibits of a large number of Kenyon Cells (KCs). We

employed available antenna recordings [2] and focus only on 23 glomeruli, and hence Projection Neurons (PNs) in the AL. In the Calyx, the number of KCs as well as the connectivity between PNs and KCs are both parametrized to study the effect of the degree of connectivity in the Calyx. The DNPs modeling the functional logic of the Calyx are implemented by differential DNP (dDNPs) [3]. Using a rank-based characterization of the response of the KCs as well as prior stages of the OEM, we found that the dDNPs support a representation of odorants — both individually and in mixtures — that remains largely invariant across different levels of odorant concentration and different instantiations of the random connectivity across individual flies. Furthermore, supported by this invariance, we show that the KC representation preserves odorant identity and demonstrate how it can be recovered. These findings offer new insights onto modeling the representation and processing of odorant mixtures using dDNPs as canonical models of computation within the EOS as well as other early sensory systems of the fruit fly.
[1] Lazar & Zhou (2023) Biol Cybern DOI: 10.1007/s00422-023-00972-x
[2] Lazar, Liu & Yeh (2023) PLOS Comput Biol DOI: 10.1371/journal.pcbi.1011043
[3] Münch & Galizia (2016). Sci. Reports DOI: 10.1038/srep21841

Disclosures: A.A. Lazar: None. **T. Liu:** None. **C. Yeh:** None. **Y. Zhou:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

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Topic: D.03. The Chemical Senses

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Richard and Susan Smith Family Award for Excellence in Biomedical Research
Klingenstein-Simons Fellowship Award in Neuroscience
Yale University School of Medicine, Brown-Coxe Fellowship
NIH grant R01DC018570

Title: Combinatorial Integration and Inhibition in an Olfactory Circuit

Authors: *K. LIZBINSKI[1], J. M. JEANNE[2];
[2]Neurosci., [1]Yale Univ., New Haven, CT

Abstract: Neural circuits route sensory information across multiple synaptic layers to extract, amplify or disregard relevant properties of a stimulus. For example, many higher-order circuits pool information from distinct presynaptic channels which may be a way to perceptually bind specific aspects of a stimulus together (i.e. odor valence). However, it has been difficult to disentangle how postsynaptic partners integrate information from their presynaptic partners and understand what stimulus properties are preserved across synaptic layers due to the numerical complexity and densely recurrent nature of many circuits. To understand how circuits combine

and refine combinatorial synaptic input, we have investigated how higher-order olfactory neurons of the fruit fly, *Drosophila* integrate odor information from identified, presynaptic partners. We use this model because the first two stages of neural circuits are well characterized, the full, anatomical connectivity between all neurons is known, and third-order neurons can be targeted with cell-type resolution. In the fly, second-order projection neurons (PNs) encode odor identity, and send odor information to the lateral horn, a higher-order olfactory region involved in innate odor preference and analogous to the cortical amygdala. PN to lateral horn neuron (LHN) connectivity is stereotyped across flies and single LHNs receive olfactory input from multiple PNs innervating distinct glomeruli. Using 2-photon calcium imaging, we created a comprehensive odor-response map across PNs to a wide panel of odors. To predict how LHNs of interest integrate PN input, we linearly summed PN response magnitudes from relevant glomeruli to specific odors and scaled response predictions based on the known synaptic connectivity between these same PNs and specific LHNs. LHN odor responses were more sparse than predictions based on feedforward PN excitation alone. Both PN axons and LHNs receive anatomical input from GABAergic neurons, suggesting inhibition may shape LHN odor responses. Localized GABA disruption during odor stimulation revealed that GABA significantly sparsens the responses of some LHN types while preserving odor responses in others. LHNs also exhibited heterogenous temporal response patterns: some responded with brief increases in calcium at odor onset, while others had long-lasting calcium responses extending far past odor offset. Together, our results suggest that LHNs are not simply linear encoders of feedforward excitation, GABA significantly shapes LHN odor representations, and that as a population, LHNs use a diverse chemotemporal code to represent more complex aspects of olfactory stimuli.

Disclosures: K. Lizbinski: None. **J.M. Jeanne:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

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Topic: D.03. The Chemical Senses

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Richard and Susan Smith Family Award for Excellence in Biomedical Research
Klingenstein-Simons Fellowship Award in Neuroscience
Innovative Research award from the Kavli Institute for Neuroscience at Yale University

Title: Temporal odor processing in Drosophila melanogaster mushroom body

Authors: *P. MISHRA, J. M. JEANNE;
Dept. of Neurosci., Yale Univ., New Haven, CT

Abstract: Past experiences impact future choices and decision-making capabilities of an animal. The temporal pairing of sensory information can form positive or negative associations that can be crucial for survival. Animals need to detect the changes in temporal profile of stimuli and learn to swiftly adapt. Hence, it is important to distinguish between subtle differences in stimulus timing. The parameters that define olfactory stimuli include odor identity, concentration, spatial localization and temporal patterns. The olfactory circuit of *Drosophila melanogaster* provides an ideal system to investigate temporal processing of stimuli. The *Drosophila* mushroom body, a higher-order processing center is known for sparse coding - where odors are encoded by distinct, non-overlapping patterns of neural activity resulting in pattern separation between odors. But how the mushroom body decodes and utilizes temporal information embedded in its input is not well explored. We aim to leverage the tractability of *Drosophila* to mechanistically understand how dynamic temporal information is processed by biological neural networks to generate precise behavioral responses. To examine the population response of Kenyon cells (KCs; the intrinsic neurons of the mushroom body) to odor input with varying temporal pattern, we first employed the genetically encoded voltage indicator ArcLight in two-photon imaging setup, which allowed us to gain high temporal resolution. Our preliminary results indicate that peak response of different KC populations is tuned to different phases of a 2 second odor pulse (onset, duration and offset). Interestingly, temporal tuning properties varied across KC subtype, odor identity and specific temporal patterns of odor presentation. These observations suggest that the mushroom body is actively involved in temporal odor processing. Next, to gain insights into how this temporal response diversity regulates associative learning, we employed two-photon calcium imaging from KCs. We monitored and compared the response of different KC subtypes to two different odors presented before and after a classical pairing protocol (with different temporal patterns). We observed changes in response amplitude and shift in response kinetics, providing initial lines of evidence that mushroom body circuit discerns temporal differences associated with different odor combinations.

Disclosures: P. Mishra: None. **J.M. Jeanne:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

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Topic: D.03. The Chemical Senses

Support: NSF NCS CBET-2123862
NSF EFRI BRAID EFMA-2223811
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The Eric and Wendy Schmidt AI in Science Postdoctoral Fellowship, a Schmidt Futures Program

Title: Hierarchical Learning and Denoising with an Olfaction-Inspired Neuromorphic Network

Authors: *R. MOYAL[1], M. EINHORN[1], A. BORTHAKUR[2], T. A. CLELAND[1];
[1]Cornell Univ., Ithaca, NY; [2]Data Sci. and Artificial Intelligence, IIT Guwahati, Guwahati, India

Abstract: The goal of odor source separation and identification from real-world data presents a challenging problem. Both individual odors of potential interest and multisource odor scenes constitute linear combinations of analytes present at different concentrations. The mixing of these analytes can exert nonlinear and even nonmonotonic effects on cross-responsive chemosensors, effectively occluding diagnostic activity patterns across the array. Neuromorphic algorithms, inspired by specific computational strategies of the mammalian olfactory system, have been trained to rapidly learn and reconstruct arbitrary odor source signatures in the presence of background interference. However, such networks perform best when tuned to the statistics of well-behaved inputs, normalized and predictable in their activity distributions. Deployment of chemosensor arrays in the wild exposes these networks to disruptive effects that exceed these tolerances. To address the problems inherent to chemosensory signal conditioning and representation learning, the olfactory bulb deploys an array of strategies: (1) shunting inhibition in the glomerular layer implements divisive normalization, contributing to concentration-invariant representations; (2) feedforward gain diversification (synaptic weight heterogeneity) regularizes spiking activity in the external plexiform layer (mitral and granule cells), enabling the network to handle unregulated inputs; (3) gamma-band oscillations segment activity into packets, enabling a spike phase code and iterative denoising; (4) excitatory and inhibitory spike timing dependent learning rules induce hierarchical attraction basins, enabling the network to map its highly complex inputs to regions of a lower dimensional manifold; (5) neurogenesis in the granule cell layer enables lifelong learning and prevents order effects (regularizing the learned synaptic weight distribution over the span of training). Here, we integrate these motifs into a single neuromorphic model, bringing together prior OB-inspired model architectures. In a series of simulation experiments including real-world data from a chemosensor array, we demonstrate the network's ability to learn and detect complex odorants in variable environments despite unpredictable noise distributions.

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Poster

PSTR341: Olfaction: Higher-Order Circuits

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Topic: D.03. The Chemical Senses

Support: OIST corporation

Title: Distributed processing of sensory information in odour-guided delayed action and working memory tasks

Authors: *J. K. REINERT, J. REUSCHENBACH, **I. FUKUNAGA**;
Okinawa Inst. of Sci. and Technol., Onna, Japan

Abstract: Olfactory signals are processed in multiple stages in the brain, resulting in progressive transformation of information content from predominantly sensory representations to one that has characteristics of motor commands. Odour-evoked responses in central regions like the orbitofrontal cortex or the anterolateral motor cortex exhibit pronounced modulations, which correlate tightly with decision variables. To understand fully the nature and mechanisms of this central sensory-to-motor transformation, we aimed to map the higher cortical areas involved in information processing by *in vivo* olfactory behaviour, optogenetic perturbations and molecular mapping.
We first aimed to identify the subregion of the striatum involved in acquired olfactory behaviour, as previous studies have shown its involvement in sensory-motor transformations. We used mice expressing the opsin channelrhodopsin-2 (ChR2) in GABAergic interneurons to perturb selected brain regions during both Go/No-Go odour discrimination as well as a delayed non-match to sample (DNMS). In the Go/No-Go task, perturbing the ventro-lateral striatum prior to delivery of a water reward impaired the ability to generate anticipatory licks for rewarded stimuli (auROC non-opto: 0.49, opto: 0.24, $p<0.0001$, n=17). In the DNMS task, perturbing during the inter-odour delay had a similarly grave impact (auROC non-opto: 0.44, opto: 0.05, $p<0.0001$, n=6). Yet, when mice were tasked with pressing a lever to obtain the reward, perturbation of the same striatal region had a smaller effect on lever presses compared to anticipatory licks (auROC licks non-opto: 0.51, opto: 0.28, $p=0.0458$; auROC lever non-opto: 0.51, opto: 0.46, $p=0.6642$, n=4). Together this suggests that this striatal sub-region is essential for processing reward-related sensory input specifically for the generation of anticipatory licks but not the motor patterns involved in lever presses.
To clarify what higher brain regions are involved in this specific odour-to-motor transformation, we used retrograde AAV tracing to map brain regions connected to our target striatal subregion combined with c-fos staining in odour exposed animals to reveal brain regions involved in processing odour information. Using this approach, we identified several central brain regions that are both directly connected to our target striatal sub-region as well as activated upon odour presentation.
Taken together, we have identified a central brain region critically involved in sensory-motor transformation as well as anatomically connected regions. Our study may serve as a crucial step towards comprehensive understanding of central olfactory representations.

Disclosures: J.K. Reinert: None. **J. Reuschenbach:** None. **I. Fukunaga:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

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Topic: D.03. The Chemical Senses

Support: NIH Grant U19NS112953
NIH Grant F31 DC 20373-2

Title: Respiration coordinates the olfactory cortical code

Authors: R. M. BLAZING[1], K. M. FRANKS[2];
[1]Duke Univ., Durham, NC; [2]Neurobio., Duke Univ., Durham, NC

Abstract: In the brain, information is often encoded spiking activity relative to oscillatory dynamics. For example, in the hippocampus, a location's proximity is encoded by place cell spiking relative to the theta cycle. Downstream circuits must read out this phase code to guide navigation. In the olfactory bulb (OB), odor identity is encoded in the timing of glomerular responses relative to the respiration cycle. Computational studies indicate that phase-locking of cells in the piriform cortex (PCx) coordinates the readout of phase-coded information from the OB to support odor recognition. However, there is little experimental evidence for this hypothesis. To address this question, we optogenetically stimulated glomerular-sized spots on the OB with brief light pulses at different respiration phases while recording from populations of PCx neurons in awake, head-fixed mice. PCx neurons exhibited pronounced tuning to stimulation at specific respiration phases, which was highly conserved across different spots. Moreover, across the PCx population, preferred phases uniformly tiled the respiration cycle. To determine the role of phase-locking in this phenomenon, for each cell, we computed the preferred respiration phase of spontaneous spiking activity. As hypothesized, responses to glomerular stimulation generally occurred during this preferred window, suggesting that PCx phase-locking gates the readout of phase-codes from the OB. We next performed a series of experiments to determine the circuit basis of this computation. Naris occlusion abolished PCx phase preferences, indicating their reafferent origin. Intriguingly, however, OB mitral/tufted cells exhibited weak phase tuning that was biased toward inhalation, suggesting that PCx phase tuning is an emergent cortical computation. Indeed, disrupting PCx recurrent circuitry with tetanus toxin aligned PCx phase preferences to those in the OB, demonstrating that recurrent circuits actively redistribute phase preferences within PCx. Thus, PCx circuitry transforms the OB phase code into a sparse ensemble code, enabling storage and recognition of phase-coded odor information.

Disclosures: R.M. Blazing: None. **K.M. Franks:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

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Topic: D.03. The Chemical Senses

Support: NRF-2021R1A6A3A0108733912

Title: Investigating olfactory neural circuits with multi-targeting neural probe.

Authors: *J.-K. HAN;
Korea Univ., Seoul, Korea, Republic of

Abstract: Neuroscience has long investigated neural circuits for understanding cognitive and emotional behavior. Recent developed multiregional recording techniques make it possible to discover new findings that broaden our knowledge. In particular, olfactory system has not been studied in multi-regional scale. Here, we introduce neural probe techniques with an application of study of olfactory neural circuits in freely moving rodent model. The customized neural probe successfully recorded single unit activities of hundreds of neurons. Using behavior paradigms for memory, we confirmed that multiple regions are co-activated, such as piriform cortex, insular cortex, and prefrontal area. These results suggest that these regions are integrally involved in the processing and retrieval of olfactory memories. This multi-regional approach not only confirms the interconnected nature of these cortical areas but also provides new insights into the mechanisms by which sensory information is integrated and utilized in cognitive functions. Further studies using these techniques may reveal more about the specific pathways and interactions that underlie olfactory-driven behaviors and their implications for broader neurological functions.

Disclosures: J. Han: None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

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Program #/Poster #: PSTR341.08/E36

Topic: D.03. The Chemical Senses

Support: R00 DC017754

Title: Distribution of interhemispheric projections between the anterior olfactory nucleus and the olfactory bulb

Authors: *L. R. VIVONA, J. D. ZAK;
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Abstract: Olfaction plays a key role in the daily life of both humans and animals. It contributes to feeding behaviors, mate selection, and memory. A key feature of sensation is its bilaterality. Integrating bilateral sensory information is required to evaluate the temporal and spatial structure of olfactory stimuli. However, olfactory information remains lateralized from the olfactory epithelium to the olfactory cortex, with the first interhemispheric crossing at the anterior olfactory nucleus (AON).
Although axonal projections from the AON target both the ipsi- and contralateral hemispheres, less is known about the extent and targets of AON projections to the contralateral hemisphere. In

this study, we characterized interhemispheric projections from the AON and their functional connectivity with postsynaptic targets in the olfactory bulb (OB).
First, in mice, we labeled AON neurons with AAV1.syn.turboRFP and quantified the layer-specific termination of their axon collaterals in the olfactory bulb at both the ipsi- and contralateral hemispheres. Our analysis revealed a 63.2% ± 7.6% (n = 4 mice, p = 0.04) reduction in the total density of fibers projecting to the contralateral OB; however, the relative distribution of fiber densities in each OB was similar. Next, we used a retrograde approach to characterize the spatial distribution of AON cell bodies that project to each OB hemisphere. Cholera toxin subunit B (CTb) conjugated to Alexa 647 was injected into one OB, and the cellular spatial distribution was compared in each AON. In the same experiment, we injected CTb conjugated to FITC into the opposite OB, allowing us to estimate the total number of ipsilateral (55.60 ± 0.07%), contralateral (44.40 ± 0.07%), and bilateral (4.34 ± 1.19%) projecting AON neurons. Our results indicate that most AON neurons project to either the ipsi- or contralateral hemisphere, with a small subpopulation projecting to both. As a final component of our study, we characterized the functional connectivity between the AON and the ipsi- vs. contralateral OBs. AAV1.syn.ChR2.YFP was injected unilaterally into the AON, and functional connectivity was assessed by measuring light-evoked postsynaptic currents at granule cells in the OB. We found robust light-evoked monosynaptic excitatory and polysynaptic inhibitory currents in the ipsilateral hemisphere; however, synaptic responses in the contralateral hemisphere were sparse and smaller in amplitude, consistent with our anatomical observations. Our future studies will focus on understanding how the projection patterns and functional connectivity from the AON to the OB contribute to interhemispheric comparisons of olfactory stimuli.

Disclosures: L.R. Vivona: None. **J.D. Zak:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.09/E37

Topic: D.03. The Chemical Senses

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European Synchrotron Radiation Facility, beamline ID16A proposal
p94388 / LS3231

Title: Structure-function analysis of mouse olfactory bulb circuits using X-ray nano-holotomography

Authors: *Y. ZHANG[1,2], C. BOSCH PIÑOL[1], T. ACKELS[1], A. LAUGROS[3], A. BONNIN[4], J. LIVINGSTONE[3], C. WALTENBERG[5], M. BERNING[6], M. KOLLO[1], A. NATHANSEN[6], N. RZEPKA[6], P. CLOETENS[3], A. PACUREANU[3], A. T. SCHAEFER[1,2];
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Abstract: Information is relayed between brain areas by often parallel streams. Neurons might share common inputs yet convey distinct information to overlapping downstream targets. Dissecting how functional properties relate to these anatomical features is often hampered by scale mismatch: Densely defining anatomical association requires subcellular resolution across mm^3 volumes. Here, we leverage the anatomical organisation of the mouse olfactory bulb where dozens of projection neurons (mitral and tufted cells, M/TC) are affiliated with a single input unit, a glomerulus. While sharing common input they are thought to represent different processed versions of this input that are relayed to overlapping postsynaptic targets. To link functional properties of projection neurons to their anatomical glomerular association, we combine *in vivo* two-photon imaging with synchrotron µCT anatomical analysis of 8mm3 and targeted X-ray nano-holotomography (XNH) of 0.4mm^3 tissue volumes. New developments in XNH enable us to reliably identify subcellular features and automatically segment ~80,000 cell nuclei in the acquired X-ray tomography volume. The high resolution and signal-to-noise ratio make it possible to integrate XNH into a multimodal correlative imaging pipeline to identify several 100 functionally imaged projection neurons in the anatomical dataset and their detailed anatomical structure, including up to 20 projection neurons associated with an individual glomerulus (“sister” cells). In three biological replicates we find consistently that overall odour response profiles to a panel of 47 monomolecular odours are strikingly conserved between sister cells, with MCs showing slightly more diversification than TCs. Moreover, while response magnitude is conserved, temporal response profiles can vary robustly between sister cells. This demonstrates that odour identity information relayed from a glomerular module is broadcasted in sync to downstream areas using the temporal response structure as a substrate to convey possibly channel-specific features. Thus, synchrotron X-ray tomography in general and XNH in particular can reliably link subcellular anatomical structure to function in a non-destructive way across the mm^3 scale. With recent advances in X-ray optics and the emergence of 4th generation synchrotrons, it becomes conceivable to extend this approach to entire brain regions with increasing resolution.

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Poster

PSTR341: Olfaction: Higher-Order Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.10/E38

Topic: D.03. The Chemical Senses

Support: NIDA Training Grant T90DA059109/R90DA060338
Brain Initiative RF1NS133598

Title: Behavioral analysis of mice sequentially trained on freely-foraging and virtually-navigating olfactory discrimination tasks

Authors: *Z. WANG, A.-M. M. OSWALD;
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Abstract: Whether the mice can generalize prior sensory knowledge across tasks with different behavioral contexts remain unknown. In this project, we will train the mice sequentially on two tasks that have different behavioral contexts. In the first task, mice freely forage in an open arena. In the second, they are head-fixed and navigate on a virtual track. In both tasks, mice learn to discriminate between odor pairs for water rewards. We first trained the mice on the foraging task which mice learn within 1-3 days of training on average. We then train them on the virtual navigation task which requires 21 days of training on average. In this study, we ask three questions. First, do mice transfer the odor-reward knowledge from the easy task to the harder task? And, if so, does this improve performance on the harder task? Does this require simply experience or learned association of odor and reward? We will train three groups of animals: (1) Mice that learn to discriminate two odors in the foraging task and then learn to discriminate the same odors during virtual navigation. (2) Mice that learn to discriminate odors in the first task but then learn to discriminate two different odors in the second. (3) Mice that are habituated but don't learn to discriminate any odors in the first task, but then learn to discriminate the same odors in the second task. We will investigate whether the knowledge of the exact odor-reward associations can be transferred between the two tasks and improve performance by comparing groups (1) and (2). We will then investigate whether learning the behavioral relevance (reward contingency) is required for knowledge to be transferred between the two tasks by comparing groups (2) and (3). This project is the first phase of an ongoing project to understand how odor information is represented in piriform cortex across behavioral tasks.

Disclosures: Z. Wang: None. **A.M. Oswald:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

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Topic: D.03. The Chemical Senses

Support: BRAIN Initiative, 1RF1NS133598

Title: Vasoactive intestinal polypeptide (VIP)-expressing interneurons in piriform cortex

Authors: *C. SUN, A.-M. M. OSWALD;
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Abstract: Synaptic plasticity in the anterior piriform cortex (APC) plays a key role in the formation of cortical assemblies during olfactory learning. Pairing afferent input from olfactory bulb with activation of local recurrent input in APC strengthens the intracortical excitatory synapses through long-term potentiation (LTP). Previous studies in our lab have shown that excitatory synaptic plasticity in APC is gated by vasoactive intestinal polypeptide (VIP)-expressing interneurons via VIP-SST-PN disinhibitory circuitry. However, little is known about VIP interneurons physiology in APC, and cortical regions broadly. In this study, we aim to characterize the VIP interneuron heterogeneity and reveal how VIP interneurons are recruited to participate in the disinhibitory circuit motif. Using *in vitro* whole-cell patch clamp with optogenetics in VIP-Cre/tdTomato transgenic mice, we recorded VIP interneurons in L2 and L3 of APC slices. The electrophysiological properties of the VIP interneurons are parametrized and used for classification and clustering. The preliminary result shows that VIP interneurons in APC present heterogeneous firing properties including a) irregular spiking, b) continuous adapting, c) burst adapting and d) fast spiking. The difference in adapting firing pattern of VIP interneurons may suggest different roles in time-dependent regulation of cortical activity. We hypothesize that the recruitment of distinct subtypes of VIP interneurons involves different combinations of electrical drive and neuromodulation. Our findings will provide valuable insight for the role and mechanism of VIP interneurons across cortex, which is crucial in understanding attention, sensory learning and memory.

Disclosures: C. Sun: None. **A.M. Oswald:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

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Program #/Poster #: PSTR341.12/E40

Topic: D.03. The Chemical Senses

Support: RF1NS133598

Title: An inhibitory circuit mechanism for discrimination learning in the olfactory cortex

Authors: *S. POSTLEWAITE[1], K. E. FRIASON[2], C. MIEHL[1], A.-M. M. OSWALD[1], B. DOIRON[1];
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Abstract: In the piriform cortex (PCx), odors are represented by the sparse and distributed activity of unique neural populations. It is theorized that groups of co-active neurons with strong connectivity, labeled neuronal assemblies, are a basic unit of representation and form based on synaptic plasticity mechanisms. Here, we asked whether assembly formation occurs in the mouse PCx after learning an odor discrimination task. In this task mice must choose between two simultaneously presented odor mixtures in which one mixture is rewarded. Notably, the rewarded mixture is composed of the same set of components as the unrewarded mixture but with an additional compound. Preliminary evidence from our group suggests an assembly emerges for the rewarded mixture, but not for the unrewarded mixture. Subsequent behavioral testing indicates mice have learned to associate the unique component in the rewarded mixture with the reward instead of the mixture as a whole, suggesting assembly formation specific to that component. We extend these findings by developing a spiking neural network with spike-timing dependent plasticity (STDP) rules to computationally explore the circuit mechanisms that could underlie these experimental findings. Our model demonstrates that several distinct inhibitory populations are required to simultaneously stabilize spiking dynamics of formed assemblies and gate synaptic plasticity. These results corroborate our recent experimental work suggesting a disinhibitory circuit mechanism for gating excitatory synaptic plasticity (Canto-Bustos et al., 2022). Furthermore, we show strong lateral and weak feedback inhibition is crucial for suppressing the representation of the overlapping components while allowing assembly formation for the unique component. This lateral inhibitory motif can emerge spontaneously when incorporating an inhibitory STDP rule and co-tuned excitatory and inhibitory populations. As our model is not unique to the olfactory cortex, these results imply a general mechanism for discrimination learning in the brain.

Disclosures: S. Postlewaite: None. **K.E. Friason:** None. **C. Miehl:** None. **A.M. Oswald:** None. **B. Doiron:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.13/F1

Topic: D.03. The Chemical Senses

Support: RF1NS133598

Title: Inhibitory synaptic plasticity in piriform cortex

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Abstract: The anterior piriform cortex (APC) is thought to be a site of odor encoding. The proximity to odor sensory input makes the APC highly tractable for dissecting the role of cortical circuitry in sensory processing. However, the trilaminar circuit structure of the APC is similar to that of the hippocampus, suggesting a potentially associative role in learned odor representations. Indeed, associative long-term potentiation (LTP) can be elicited using a standard LTP paradigm. However, it is not known if there is commensurate plasticity at inhibitory synapses with APC. We investigated excitatory and inhibitory synaptic plasticity in APC following criterion performance in an olfactory discrimination task. We used targeted recombination in active populations (TRAP) to conditionally express tdTomato in pyramidal neurons (PNs) that were active during the task. We found that in trained animals, recurrent excitation and inhibition are potentiated in tdTom+ neurons compared to tdtom- neurons. To investigate the synaptic locus of inhibitory plasticity, we bred triple transgenic mice that allow TRAP expression in PNs along with cre-dependent ChR2 expression in parvalbumin (PV) or somatostatin (SST) interneurons (IN). Following learning, we then recorded light evoked inhibitory currents onto tdtom+ and tdtom- neurons in APC. We found that PV mediated inhibition tended to be stronger onto tdtom+ PNs compared to tdtom- PNs while SST-mediated inhibition trended weaker or unchanged. Finally, we investigated whether PV or SST mediated inhibitory plasticity could be elicited through an associative LTP protocol. To selectively recruit PV or SST inhibition we expressed ChR2 in PV or SST INs and evoked IPSCs pre and post LTP induction. This standard associative LTP paradigm requires $GABA_A$ receptor blockade during induction. This would impair assessment of IPSCs. We have previously shown this could be circumvented by optically driving interneurons that express vasoactive intestinal polypeptide (VIP) during induction. VIP INs inhibit both SST and PV INs but are not sufficiently activated by TBS stimulation without additional external drive. We surmise that cholinergic activation might sufficiently increase VIP IN excitability during TBS. We applied cholinergic agonists during induction and assessed changes in EPSC and IPSC amplitudes 45 min following induction compared to baseline. We found that the muscarinic agonist, carbachol, differentially affected PV and SST mediated IPSCs at baseline. However, carbachol did not promote LTP of EPSCs or IPSCs, contrary to previous reports. Ongoing experiments investigate whether nicotinic receptor agonists could promote LTP.

Disclosures: K.E. Friason: None. **A.M. Oswald:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

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Topic: D.03. The Chemical Senses

Support: NIH Grant R01 DC007703-18W1

Title: Temporal dynamics of gustatory-olfactory cortical processing in rats

Authors: *T. GRAY[1], I. GOLDSTEIN[2], D. B. KATZ[3];
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Abstract: The basic characteristics underlying how olfactory and gustatory sensory modalities interact are not well understood. We compared the single-neuron and population responses of the cortical regions that process these senses in rats in order to understand how taste and smell work together during consummatory behaviors. Rats learn odor-taste associations more robustly when they are delivered at the same time and via the same route (the mouth) than when odors are delivered to nose at the same time that a taste is delivered into the mouth. The cortical regions that process taste and smell, gustatory cortex (GC) and piriform cortex (PC) respectively, are specifically influenced by each other even without stimuli. The temporal responses of GC and PC chemosensory neurons are modulated by which route the odor is delivered; retronasally (into the mouth) versus orthonasally (into the nares). Coactivation is particularly stronger when both taste and smell are delivered intraorally than either stimulus alone. This synergistic effect is diminished when they are delivered via separate routes or at different times. Our work highlights specific characteristics of chemosensation at the cortical level and how flavor networks are differentially coactivated during consummatory behaviors.

Disclosures: T. Gray: None. **I. Goldstein:** None. **D.B. Katz:** None.

Poster

PSTR341: Olfaction: Higher-Order Circuits

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR341.15/F3

Topic: D.03. The Chemical Senses

Support: Department of Biomedical Sciences Funds

Title: Novel background odors destabilize glomerular output representations in two mouse models of autism

Authors: K. STURM, Z. SCHEIER, G. H. OTAZU;
New York Inst. of Technol., Col. of Osteo. Med., Old Westbury, NY

Abstract: Novel stimuli can increase stress in individuals with autism but the neural mechanism for this "insistence on sameness" is not clear. *Cntnap2*$^{-/-}$ and *Shank3B*$^{-/+}$ mouse models of autism have target odor recognition deficits in novel background odors despite a similar performance to wild-type in familiar backgrounds (Li et al., 2023, Ryndych et al., 2023). It is unclear why a

novel background odor has such disproportionate behavioral impact nor how these mice mitigate background odor impact with experience. To investigate the role of the olfactory bulb output, we expressed GCaMP6f in mitral and tufted cells in *Shank3B* mice and *Cntnap2* mice and we performed widefield calcium imaging. Four water-deprived *Shank3B*$^{-/+}$ and four *Cntnap2*$^{-/-}$ mice were trained to identify odors in the presence of background odors using a go/no-go behavior, in which they were required to lick a waterspout for the go target odor and refrain from licking for the no-go stimuli. We used catch trials where one of the background odors was replaced by a novel background odor. The novel background odors were delivered 750 ms before, and throughout the presentation of the target odors. Error trials had significantly (p=0.0151, double tailed paired t-test) larger average glomerular responses (z_score 0.76±0.08, n=37 odors mixtures) compared the glomerular activation of correct trials (z_score 0.59±0.06). The discriminability of glomerular representations during the target presentation that were preceded by large response background response was also reduced compared to trials with smaller novel responses indicating that large glomerular responses produced by background odors affected the behavior and destabilized the neural representation of the targets. We analyzed the responses as background odors transitioned from novel to known. Throughout training as the mice became better at discriminating the odor mixtures, glomerular representations became more distinct as well as more stable. Further, after training, the glomerular representations of the background odors were suppressed resulting in even more distinct and less variable target mixture responses. This contrasts with the wild type mice (n=3) where this suppression was not found, and the variability of naïve WT mice was similar to the variability of *Shank3B*$^{-/+}$ and *Cntnap2*$^{-/-}$ expert mice. Large olfactory bulb output produced by novel odors negatively affected odor coding of target background mixtures. Mouse models of autism used a strategy to suppress excess glomerular activity permitting improved target recognition and more discriminable mixture representation as a background odor transitioned from being novel to being known.

Disclosures: K. Sturm: None. **Z. Scheier:** None. **G.H. Otazu:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.01/F4

Topic: D.05. Auditory and Vestibular Systems

Support: NIDCD Grant DC007690
NINDS BRAIN Initiative Grant NS132812

Title: Hearing Ghosts: Understanding Coding Underlying Perception of Phantom Sounds

Authors: *S. NANDI, A. BAE, R. FERGER, J. L. PENA;
Albert Einstein Col. of Med. Dominick P. Purpura Dept. of Neurosci., Bronx, NY

Abstract: Inherent to survival of many species is sound localization. Barn owls (*Tyto furcata*) are sound localization specialists and utilize binaural cues of interaural time difference (ITD) and interaural level difference (ILD) to infer horizontal and vertical locations respectively in space. These cues construct a topographic map of space in the midbrain, but the readout of this map is corruptible to a dearth of frequency information. Specifically, pure tone and narrowband frequencies originating from one location in space are perceived as originating from multiple locations, a result of the phase-locking and frequency-specific nature of ITD-inferring neurons. These additional perceived locations of a pure tone or narrowband sound are known as phantom sound sources. Behavioral studies have demonstrated that owls will head-turn towards both true and phantom sources when the sound's bandwidth is less than 3 kHz. Similarly, electrophysiological studies of the optic tectum (OT), a part of the midbrain containing the topographic map of space, have demonstrated that side peak suppression, a phenomenon necessary for accurate sound localization, does not occur when the sound's bandwidth is less than 3 kHz. However, these studies were performed using a single electrode in a single part of the map, while pure tones and narrowband sounds activate multiple parts of the map. Additionally, activation of multiple components of the map invokes the midbrain stimulus selection network to determine the most salient stimulus for further processing. Further, information across OT is biased by upstream frequency-ITD preferences, calling into question the equality of responses to pure tones and narrowband sounds across the map. Thus, we propose using a multi-electrode array to concurrently observe responses to pure tones and narrowband sounds across the OT map, and hypothesize excitation of responses at ITDs whose frequency preferences include the frequency of the stimulus, and suppression of responses at ITDs whose frequency preferences do not include the frequency of the stimulus.

Disclosures: S. Nandi: None. **A. Bae:** None. **R. Ferger:** None. **J.L. Pena:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

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Program #/Poster #: PSTR342.02/F5

Topic: D.05. Auditory and Vestibular Systems

Support: Wellcome Trust WT108369/Z/2015/Z

Title: Spatial response properties of inferior colliculus neurons during experience-dependent adaptation to asymmetric hearing

Authors: A. I. SANCHEZ JIMENEZ, V. M. BAJO-LORENZANA, B. D. B. WILLMORE, A. J. KING, ***F. R. NODAL**;
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Abstract: The ability, through training, to overcome the impairment in sound localization caused by asymmetric conductive hearing loss is well documented. Research in ferrets wearing an earplug has established that such experience-dependent plasticity requires a functioning auditory cortex and the integrity of its descending circuits to the inferior colliculus (IC). Here, we examined whether behavioral adaptation to asymmetric hearing loss is associated with changes in IC response properties. We recorded from the IC bilaterally using high-density Neuropixels probes over several weeks in three ferrets that were performing a sound localization task in the azimuthal plane. Ferrets were rewarded for approaching and licking a spout below the target speaker, and the spatial tuning properties of IC neurons were explored using broadband sounds. The location of the probes inserted dorsoventrally into the IC was determined physiologically and anatomically by recording neuronal frequency response areas under sedation and histological inspection, respectively. Most of the recordings were in the central nucleus of the IC, with some recording sites in its dorsal and lateral cortices. Under normal hearing conditions, the most common responses were primary-like and sustained. Most neurons (77.12 ± 14.89%) had a contralateral preference (mean centroid for left IC: 54.08 ± 12.84°, right IC -42.99 ± 45.48°), with a broad equivalent rectangular receptive field (ERRF) (145.77 ± 7.83°). No differences between left and right IC were observed. Moreover, a population linear decoding model was able to decode the stimulus azimuth from IC activity highly accurately, with greater accuracy in the left-right axis than in the front-back axis. The contralateral preference and broad spatial tuning of IC neurons are consistent with opponent two-channel coding of sound location. Plugging one ear produced a marked change in the response properties of IC neurons. Neurons ipsilateral to the earplug exhibited a broadening of their spatial tuning (larger ERRF) and a reduced contralateral preference, whereas neurons contralateral to the earplug exhibited a profound suppression of their activity. During behavioral adaptation to unilateral hearing loss, we observed a small reduction in ERRF in the IC ipsilateral to the earplug and increased spatial modulation of responses in the contralateral IC, though these changes were not sufficient to restore normal spatial tuning. Nevertheless, the population decoding model showed a progressive improvement in decoding performance over the course of training, indicating that a neural correlate of behavioral adaptation is found in the IC.

Disclosures: A.I. Sanchez Jimenez: None. **V.M. Bajo-Lorenzana:** None. **B.D.B. Willmore:** None. **A.J. King:** None. **F.R. Nodal:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

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Program #/Poster #: PSTR342.03/F6

Topic: D.05. Auditory and Vestibular Systems

Support: HK GRF Project 11101020
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MedEl

Title: Sensitivity of inferior colliculus to interaural time and level differences in neonatally deafened rats

Authors: *M. ZEESHAN[1], F. PENG[2], B. CASTELLARO[2], S. FANG[2], N. ROSSKOTHEN-KUHL[3], J. W. SCHNUPP[4];
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Abstract: Bilateral cochlear implants (biCIs) are increasingly used to treat severe hearing loss. However, human biCI users usually exhibit relatively poor binaural cue sensitivity, with interaural time difference (ITD) sensitivity in prelingually deaf patients being particularly poor. To better understand these shortcomings in prosthetic binaural hearing, it would be helpful to know what the “innate” ITD and ILD sensitivity of the neonatally deafened (ND), mature mammalian auditory pathway is like, but this cannot easily be investigated in humans. We therefore recorded neural responses in the inferior colliculus (IC) of rats deafened by i.p. kanamycin injection. When the deaf rats reached maturity (>p60) they were urethane anesthetized and implanted with biCIs. IC multiunit responses to pulse train stimuli at rates of 1, 100, and 900 pps with combinations of ITD $\in \pm\{0, 0.04, 0.08, 0.12\}$ ms and ILD $\in \pm\{0, 1, 4\}$ dB were recorded extracellularly, and analyzed for ITD or ILD. At pulse rates of 1, 100, and 900 pps, 85.6%, 99.7% and 97.2% respectively of multiunits were significantly ITD sensitive (Kruskal-Wallis tests), 88.5%, 96.4% and 88% were ILD sensitive, and 76.8%, 96.1% and 85.5% were sensitive to both. Sensitivity to small electrical stimulus ITDs and ILDs was therefore very widespread in the IC of adult, hearing-inexperienced, acutely CI-stimulated ND rats. While most multiunits showed significant sensitivity to both cues, examining the proportions of variance explained by ITD or ILD respectively revealed that multiunits in the naive IC nevertheless form two distinct clusters that are either predominantly ITD sensitive or predominantly ILD sensitive.

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Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

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Program #/Poster #: PSTR342.04/F7

Topic: D.05. Auditory and Vestibular Systems

Support: General Research Fund - grant # 11101020

Title: Sensitivity to envelope and pulse timing interaural time differences in prosthetic hearing

Authors: *S. FANG[1], F. PENG[2], B. CASTELLARO[2], M. ZEESHAN[3], N. ROSSKOTHEN-KUHL[4], J. W. SCHNUPP[5];
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Abstract: Binaural cues, such as interaural time difference (ITD), play a crucial role in localizing sound sources in the auditory system. However, contemporary cochlear implant (CI) processors use a coding strategy that only conveys the ITD information contained in the envelope of the sound (envelope ITD) to the cochlear implant (CI) user. As a result, the ITD information contained in the temporal fine structure of the sound (pulse-timing ITD) is not transmitted, which may contribute to the poor spatial hearing perception of CI users.To investigate the sensitivity of CI-implanted rats to envelope and pulse timing ITD, we designed a stimulus comprising a 900pps pulse train modulated by a 20 Hz sine envelope in which pulse timing ITD (PT_ITD) and envelope ITD (ENV_ITD) could vary independently from the values {-0.1, 0, 0.1 ms}. We recorded neural activity from the inferior colliculus (IC) of anesthetized neonatal deafened rats using a multi-channel silicon probe. For each multi-unit, we first applied an average template subtraction method to remove electrical artifacts, and then computed the analog multi-unit activity (AMUA) over the onset response window (0-50 ms) and the baseline window (150-200 ms). Any multi-unit with a peak amplitude in the onset window AMUA larger than the average plus 5 times the standard deviation of the baseline window AMUA was identified as responsive to the CI stimulation. For every responsive multi-unit, the proportion of variance explained by PT_ITD and ENV_ITD was computed to reveal the effect of envelope and pulse timing ITD on AMUA intensity. Our study recorded a total of 332 responsive multi-units, with 83% of them being sensitive to PT_ITD, while only one multi-unit was found to be sensitive to ENV_ITD. This indicates that CI-implanted rats exhibit far greater sensitivity to pulse timing ITD than envelope ITD. These findings suggest that the current CI stimulus strategy is not providing effective ITD information that CI users are sensitive to, and that CI users have the potential for better sound localization ability.

Disclosures: S. Fang: None. **F. Peng:** None. **B. Castellaro:** None. **M. Zeeshan:** None. **N. Rosskothen-Kuhl:** None. **J.W. Schnupp:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.05/F8

Topic: D.05. Auditory and Vestibular Systems

Support: NIH grant R00DC017472
NIH grant R01DC018284
NIH MH135565

Title: Noisy environments exacerbate hidden hearing loss induced by myelinopathy

Authors: *S. TRIPATHY[1], G. CORFAS[2], M. T. ROBERTS[3], A. H. MEHTA[4], M. BUDAK[5], V. BOOTH[6], M. R. ZOCHOWSKI[7];
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Abstract: Hidden Hearing Loss (HHL) is an auditory neuropathy leading to reduced speech intelligibility in noisy environments despite normal audiometric thresholds. We have previously shown that this could be a consequence of degraded sound localization ability. One of the leading hypotheses for such degraded performance is myelinopathy, a permanent disruption in the myelination patterns of type 1 Spiral Ganglion Neuron (SGN) cells. To model these effects, we introduce random variations in the position of heminodes in individual SGN models, which leads to a uniform phase shift in the spike trains of affected fibers. As a result, in response to a non-noisy sound tone, action potentials of different fibers lock to the sound waveform with variable phase shift, leading to decreased population locking. With addition of white noise to the sound, we find that spike times exhibit heterogeneous phase shifts, leading to a reduction in the locking of single fiber spikes to the sound waveform and further reduction of population-level locking. The effects of myelinopathy on population behavior are thus more pronounced in the presence of noise. To further test these effects on sound localization, we constructed a network model that simulates the propagation of SGN responses to cochlear nuclei and the medial superior olive (MSO) populations. We model the location of the sound impulse by introducing a time shift in the input to one ear relative to the other. We compare location discriminability in the MSO cells in the left and right hemispheres as a function of the interaural time difference (ITD) for noiseless and noisy environments. We find that the sensitivity to ITD is reduced with myelinopathy and, furthermore, that this effect is significantly exacerbated when we introduce a noisy background. In summary, our model results provide understanding of the downstream impact of SGN neuropathies.

Disclosures: S. Tripathy: None. **G. Corfas:** None. **M.T. Roberts:** None. **A.H. Mehta:** None. **M. Budak:** None. **V. Booth:** None. **M.R. Zochowski:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.06/F9

Topic: D.05. Auditory and Vestibular Systems

Support: NIH R56DC016054

Title: Developmental Regulation of Calcium Signaling in Neurons of the Mouse Medial Nucleus of the Trapezoid Body

Authors: T. TANMY[1,2], *Y. LU[1,2];
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Abstract: In the central auditory system, Ca^{2+} signaling plays a pivotal role in the regulation of cellular processes including neuronal development and maturation. Disruption of Ca^{2+} homeostasis and signaling causes abnormal development of auditory circuits, compromising auditory processing and behavior. Here, using Ca^{2+} imaging in brain slices obtained from mice that genetically expressed calcium indicator GCaMP in glycinergic cells, we investigated the underlying mechanisms for developmental Ca^{2+} regulation in neurons of the medial nucleus of the trapezoid body (MNTB), a brainstem nucleus involved in sound localization. Fluorescence images of principal MNTB neurons were obtained under excitation wavelength of 480 nm. Ca^{2+} signals were recorded in response to activation of various excitatory and inhibitory transmitter receptors through bath application of their respective agonists and under electrical stimulation applied to their afferent inputs. Prior to hearing onset at postnatal day 7 (P7), Ca^{2+} signals were produced in MNTB neurons when the glutamate receptors (NMDARs, AMPARs, group I mGluRs) were activated by bath application of their respective agonists (NMDA 200 μM, AMPA 100 μM, 3,5-DHPG 200 μM). After hearing onset (P14 and P21), the responses declined dramatically for NMDA receptors and group I mGluRs. AMPAR-mediated signals remained relatively high. In contrast, Ca^{2+} transients in response to GABA (100 μM) and glycine (200 μM) were only observed in neonatal mice and diminished a few days after birth. Transmitter receptor-mediated Ca^{2+} signaling was largely blocked by their specific antagonists. Furthermore, electrical stimulations applied to the excitatory afferent fibers innervating MNTB triggered release of glutamate which elicited Ca^{2+} signals, in a stimulus intensity- and frequency-dependent manner, via glutamate receptors and potentially voltage-gated Ca^{2+} channels. Finally, ongoing experiments will test the hypothesis that these Ca^{2+} responses are altered in a hearing loss model generated with ear plugging. Taken together, Ca^{2+} signaling in MNTB neurons was developmentally regulated and subject to refinement by hearing experience. Our work was supported by NIH/NIDCD R56DC016054.

Disclosures: T. Tanmy: None. **Y. Lu:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.07/F10

Topic: D.05. Auditory and Vestibular Systems

Support: R01 DC-013543

Title: Neurophysiology of virtual melody

Authors: *M. GONZALES[1], K. C. BACKER[1], A. SANTOYO[2], H. BORTFELD[3], A. J. SHAHIN[4];
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Abstract: Binaural Beats occur when each ear receives a tone that is a few Hz above or below the tone received by the other ear. When the two inputs combine in the brain stem, a beating sound (usually below 20 Hz) is produced, which reflects the difference between the two frequencies. Given that the human ear cannot perceive sounds below 20 Hz from the environment, it has been posited that this internally generated beating sound stimulates the brain in a way that is beneficial to health. This motivated us to create music solely based on Binaural Beats. We binaurally presented tones that systematically varied in their frequency deviation over 3.5 seconds, creating a melody-like pattern. Participants listened to these sounds and control sounds, matched in acoustical properties, while undergoing electroencephalography (EEG). Participants made judgments on whether they perceived the sounds as musical/melodic or non-musical/non-melodic. Behaviorally, participants perceived the Biaural Beat stimuli as more melodic than the control stimuli. Neurophysiologically, a sustained event-related positivity, over parietal sites and spanning the duration of the stimuli, distinguished the Binaural Beat condition from the control conditions, including a Binaural Beat condition that was perceived as non-musical. Moreover, sustained increase in alpha band (8-12 Hz) oscillatory activity was also observed at parietal sites. The latter results indicates that musicality formed by Binaural Beats induce a more relaxed state, that is typically reflected by an increase in alpha activity. In short, our findings suggest that musicality created with Binaural Beats engage differential audio-motor neural networks than typical non-musical Binaural Beats, which could impact a corresponding behavioral benefit.

Disclosures: M. Gonzales: None. **K.C. Backer:** None. **A. Santoyo:** None. **H. Bortfeld:** None. **A.J. Shahin:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

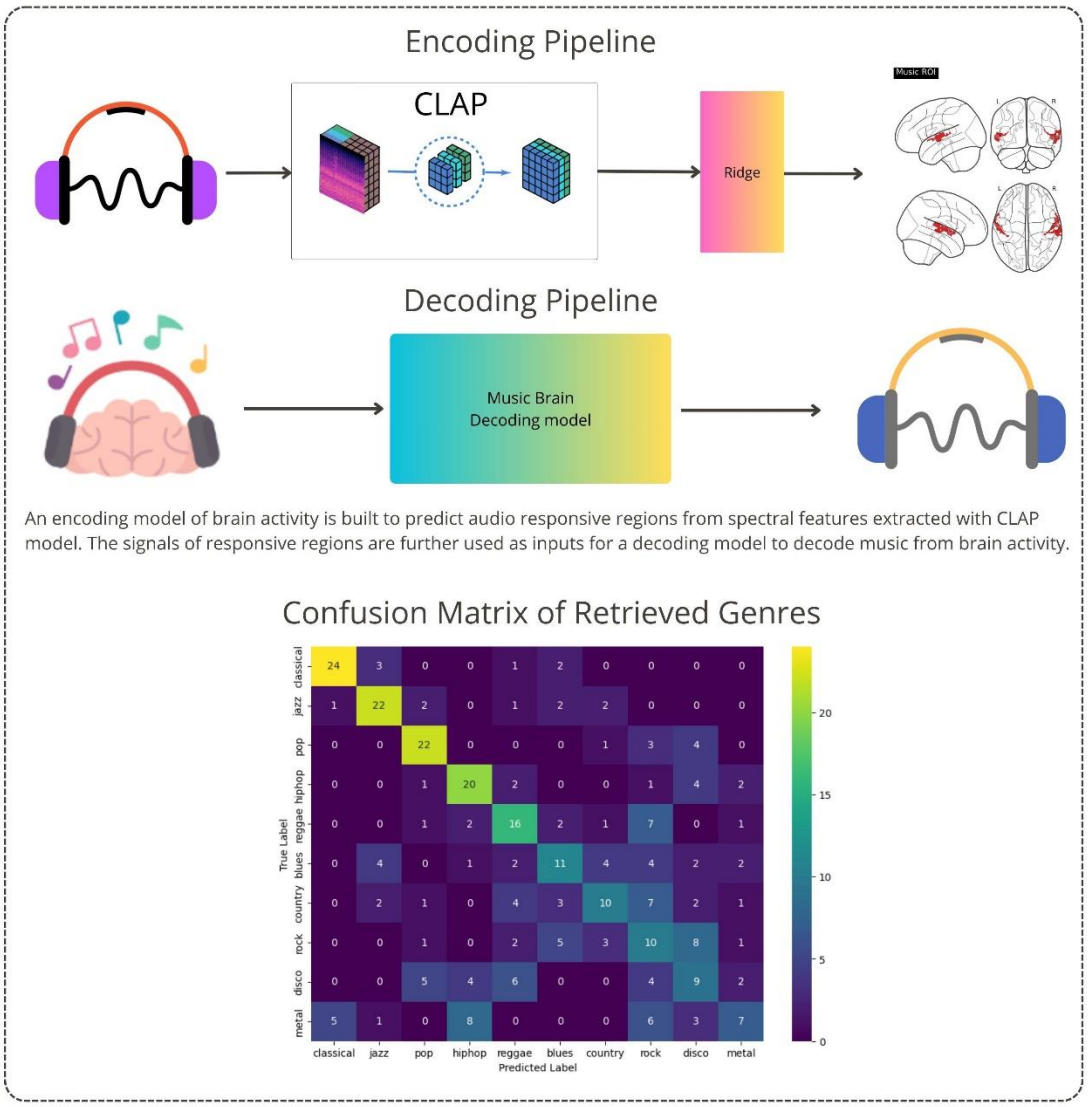
Program #/Poster #: PSTR342.08/F11

Topic: D.05. Auditory and Vestibular Systems

Title: Decoding music from brain activity: exploring the neural correlates of music perception

Authors: *M. CIFERRI, M. FERRANTE, N. TOSCHI;
Tor Vergata Univ. of Rome, Rome, Italy

Abstract: This study aims to explore the neural correlates of music perception through the "lens" of deep learning models. We leveraged the GTZen music fMRI dataset[1], which includes data from 5 subjects who listened to 540 tracks across 10 musical genres while undergoing 3T fMRI scans. We designed a deep-learning-based decoding architecture that uses the CLAP model[2], a text-audio model that converts audio into feature representations through the mel-spectrogram. The first step of our pipeline involved the identification of brain regions responsive to music. To achieve this goal, we mapped latent audio representation obtained from CLAP to average (across time points) BOLD brain activity using Ridge regression and measuring the R^2 correlation between predicted and real brain activity. A threshold of 0.1 correlation value was chosen to identify the desired ROI composed of 833 voxels.
In order to define a cross-subject decoding pipeline, the selected ROIs from the encoding step were aggregated among subjects with functional alignment to map each subject's data to a target one. We estimated by regression the audio features from the identified regions aligned, and then addressed two main tasks with those representations: - Music Genre Classification: genre prediction by multi-class Logistic regression, achieving 49% accuracy relative to the ceiling performance (88%) of the actual feature CLAP model. - Music Retrieval: comparison between predicted and actual audio representations using Nearest Neighbors in the CLAP features space, and we picked the k (k=5) closest elements as candidates. This comparison yielded an average Identification Accuracy[3] metric of 91% across subjects.
Our findings demonstrate the feasibility of decoding musical information from BOLD fMRI signal patterns only. This approach holds promise for advancing our understanding of music perception and its potential applications in music therapy, such as music-based interventions to individuals with different neurological conditions or emotional needs.



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3 Yu Takagi and Shinji Nishimoto. High-resolution image reconstruction with latent diffusion models from human brain activity. bioRxiv, 2022. doi: 10.1101/2022.11.18.517004. URL https://www.biorxiv.org/content/early/2022/11/21/2022.11.18.517004.

Disclosures: M. Ciferri: None. **M. Ferrante:** None. **N. Toschi:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.09/F12

Topic: D.05. Auditory and Vestibular Systems

Support: NSF NCS-Frontiers Award SMA-2319321
Brain Research Foundation Pilot Award BRFSG-2023-13

Title: Somatostatin Neurons Enhance Discrimination Performance in Complex Auditory Scenes

Authors: *Z. QU[1], J. NOCON[2], K. K. SEN[3], H. GRITTON[4];
[1]Bioengineering, Univ. of Illinois Urbana-Champaign, Champaign, IL; [2]Dept. of Biomed. Engin., Boston Univ., Boston, MA; [3]Biomed. Engin., Boston Univ., Boston, MA; [4]Comparative Biosci., Univ. of Illinois, Urbana, IL

Abstract: Complex auditory scenes are comprised of dynamic stimuli that can originate from multiple spatial directions and compete for listener attention. Despite the known complexity of these auditory environments, the specific mechanisms by which the auditory cortex successfully suppress competing streams remains largely unknown. Suppression of competing streams within auditory circuits is thought to depend on inhibitory networks although the cell types and circuit connectivity that supports spatial attention is not well resolved. To address this gap, we examined the role of somatostatin (SST) neurons in contributing to the neural discrimination of auditory streams in complex scenes. SST neurons are crucial for modulating pyramidal excitation and important contributors to surround inhibition, thereby influencing the dynamics of cortical activity. To understand the role of SST neurons in complex scene analysis, we created a multi-speaker environment with overlapping and competing signals allowing us to simulate a "cocktail party" like environment. Utilizing electrophysiology, optogenetics, and classifiers that utilize spike timing information to discriminate different target stimuli, we reveal that SST neurons contribute to neural sensitivity to the spatial configuration of competing sounds. These findings reveal a specialized role for SST neurons in enabling cortical circuits to discriminate auditory targets from background noise in complex auditory scenes.

Disclosures: Z. Qu: None. **J. Nocon:** None. **K.K. Sen:** None. **H. Gritton:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.10/F13

Topic: D.05. Auditory and Vestibular Systems

Support: BMBF Grant ModSynTrans

Title: The influence of synaptic noise on action potential generation and temporal filtering in lateral superior olive neurons of the auditory brainstem: a dynamic-clamp study

Authors: *J. FISCH, E. FRIAUF;
Univ. of Kaiserslautern-Landau, Kaiserslautern, Germany

Abstract: Synaptic integration is of crucial importance for inter-neuronal information transfer, and synaptic noise affects the generation of postsynaptic action potential (AP) patterns. The noise arises from two main sources: 1) varying synaptic strength of converging inputs and 2) temporal correlation of the AP activity, whether synchronized or unsynchronized. The lateral superior olive (LSO) is well suited to study excitation-inhibition integration. LSO neurons integrate differences in interaural sound pressure and temporal disparities to extract sound source information. They receive excitation and inhibition from the ipsilateral and contralateral ear, respectively. Excitation from multiple (10-40) weak input fibers is countered by few (4-8) strong inhibitory inputs. The influence of synaptic noise on the extraction of level and temporal information is unclear. Here we employed dynamic-clamp stimulation in whole-cell patch-clamp experiments on adult mouse LSO neurons. We simulated summed synaptic conductances independently for excitation and inhibition using two paradigms of presynaptic AP activity: 1) primary-like (PL), characterized by a temporally precise stimulus onset and unsynchronized sustained activity; 2) sinusoidal, simulating phase-locked afferent firing. By distributing the total excitatory and inhibitory conductances over different numbers of inputs, we analyzed the influence of synaptic noise on the output rate and the temporal precision of LSO neurons. With PL stimulation, neurons reliably encoded the stimulus onset across stimulation paradigms. Four robust excitatory inputs (10 nS each) resulted in high sustained activity (230 APs/s). This activity was virtually abolished when synaptic noise was reduced (40 inputs at 1 nS: 2 APs/s). The threshold for AP generation increased with noise reduction, suggesting inactivation of NaV channels. Surprisingly, inhibitory activity showed complex interactions with excitation. Increased inhibitory activity lowered AP thresholds, suggesting that NaV channels are released from inactivation. The effect was in opposition to the inhibitory AP-blocking effect. Spiking behavior in response to sinusoidal stimulation showed band-pass filtering, optimal at 200-500 Hz. High synaptic noise increased AP rates but decreased the temporal precision. Together, synaptic noise within the physiological range leads to strong filtering of the output rate of LSO neurons. This implies a coincidence detection mechanism, as evidenced by the band-bass filtering. Our results indicate that synchronization in the excitatory and inhibitory inputs to the LSO plays a pivotal role for sound localization.

Disclosures: J. Fisch: None. **E. Friauf:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.11/F14

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant 1RF1NS132812-01
NIH Grant R01NS135851-01

Title: A population model of the lateral shell of the central nucleus of the inferior colliculus in barn owls

Authors: *B. J. FISCHER[1], R. SYEDA[1], J. L. PENA[2];
[1]Seattle Univ., Seattle, WA; [2]Neurosci., Albert Einstein Col. of Med. Dominick P. Purpura Dept. of Neurosci., Bronx, NY

Abstract: The central nucleus of the inferior colliculus is a principal midbrain station for auditory information processing. In barn owls, the lateral shell of the central nucleus of the inferior colliculus (ICcl) plays a critical role in spatial hearing. However, responses properties of ICcl neurons are diverse and the population-level distribution of response properties and its implications for sound processing remain underexplored. To further characterize the processing of sound in the barn owl's auditory system we constructed a comprehensive population model of the ICcl in barn owls. This involved analyzing data from multiple studies to characterize response properties across various dimensions, including frequency tuning, tuning to interaural timing and level differences, temporal dynamics, intensity tuning, and response variability. We also examined correlations between these properties to understand their collective influence on auditory processing. We constructed a spiking neuron model that produces desired responses of individual neurons along these dimensions. Our model produces the desired population responses properties observed in vivo by first sampling from the empirically measured distribution of response characteristics. Then, by generating model neurons with these responses, we created a robust population-level model that reflects the diversity and complexity of auditory responses in the barn owl's ICcl. The analysis suggests that some of the diversity in responses is inherited from upstream areas, while other forms of diversity are due to variation in integrative properties of ICcl neurons. The developed model serves as a valuable tool for simulating and understanding the population dynamics of the ICcl in barn owls. It provides a foundation for future research into the integrative functions of the midbrain and forebrain in processing complex sounds.

Disclosures: B.J. Fischer: None. **R. Syeda:** None. **J.L. Pena:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.12/Web Only

Topic: D.05. Auditory and Vestibular Systems

Support: Natural Sciences and Engineering Research Council of Canada (NSERC: RGPIN-2023-03829)

Chaire Fondation Caroline Durand en audition et vieillissement de l'Université de Montréal

Title: Musical experience shapes the integration of auditory spatial cues and body representation

Authors: *D. PAROMOV, A. PAQUETTE, M. MAHEU, F. CHAMPOUX;
Univ. de Montréal, Montréal, QC, Canada

Abstract: The representation of the body in space, or body schema, results from the integration of multiple sensory inputs (vestibular, visual, somatosensory, auditory). This relationship is bi-directional, with the resulting schema influencing the processing of sensory inputs, and thus for example, auditory spatial processing. While extensive musical training is also known to modulate auditory processing, it is still unclear if it can modulate the contribution of the body schema to auditory processing, given this bi-directional relationship. This study aimed to assess the impact of the perturbation of the representation of the body in space on auditory localization in musicians. A total of 15 musicians with more than 10 years of experience and 15 non-musicians were recruited for this study. Participants were invited to perform the Fukuda-Unterberger stepping task, known to induce involuntary rotation of the body in space, with a static sound source positioned at 0-, 45-, and 90-degree azimuth as a spatial reference. Musicians error in localization error post-perturbation was significantly lesser at 0 and 45 degrees, while no differences were observed at 90 degrees, an indication that musical training can modulate the perturbator effect on auditory spatial processing. The data also provides more insight into the processes leading to the improved performance of musicians in auditory spatial processing, suggesting a higher level of stability.

Disclosures: D. Paromov: None. **A. Paquette:** None. **M. Maheu:** None. **F. Champoux:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.13/F15

Topic: D.05. Auditory and Vestibular Systems

Title: A Study into the Effects of Pinnae on Efficient Speech Denoising using Spiking Neural Networks

Authors: *R. SELAGAMSETTY[1], M. LIPASTI[2];
[1]Computer Sci., [2]Electrical and Computer Engin., Univ. of Wisconsin - Madison, Madison, WI

Abstract: Deep convolutional neural networks (CNNs) have shown great success in achieving human-like performance on speech denoising tasks, but require an exorbitant number of parameters to do so. Spiking neural networks (SNNs) present an ideal alternative due to their model size efficiency and lend themselves to be more explainable due to their biological plausibility. In this study, we incorporate delta-sigma (ΔΣ) neurons and axonal delays to build a

SNN that efficiently tackles the speech denoising task. The ΔΣ neuron model achieves efficient coding via sparse message passing, as the delta component only signals an output when a higher magnitude change is detected from the input-facing sigma component. Axonal delays allow the network to learn temporal dynamics present in speech and reflect the physiological propagation delays seen in biological axons. Prior works correlate the notches and peaks in the frequency domain introduced by the distinct morphology of ridges and curvatures of the outer ear with cues for determining elevation of a sound source along vertical planes. While the elevation-dependent notch frequencies are useful for discriminating between vertically separated tones or pulses, for signals that are more complex like speech and naturalistic noises, we find that the complete response across the frequency domain carries vital information. Our first finding is that these spectral features encoded by the pinnae provide rich transformations on the input audio such that noisy speech can be effectively denoised, even when the noise and speech are collocated to the same elevation. Our second finding in this study shows that a small, shallow spiking neural network is able to achieve state-of-the-art level denoising performance when input audio is augmented with spatial cues from human pinnae. One focus of ongoing work aims to correlate findings from our SNN to observations from early, subcortical structures in the auditory path, such as the neuronal groups in the superior olivary complex.
We use the Center for Imaging Processing and Integrated Computing (CIPIC) database containing measurements from 41 human subjects of Head Related Impulse Responses (HRIRs) to augment audio with binaural spatial cues. The Intel Neuromorphic Deep Noise Suppression Challenge speech dataset provides 500 hours of each clean speech, noise, and noisy speech inputs, for both the training and validation sets. Scale Invariant-Signal to Noise Ratio (SI-SNR) is used to evaluate audio quality. The results shown in this study warrant further investigations into understanding the role of the organization and features of the auditory ascending pathway for the task of speech denoising.

Disclosures: R. Selagamsetty: None. **M. Lipasti:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.14/F16

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant 1R15DC021563-01

Title: Horizontal localization of concurrent sound sources: an algorithm for smart hearing aids

Authors: E. FLAD[1], R. GATEWOOD[2], O. ADIGWE[2], I. GOKCEN[2], *Y. GAI[3];
[1]St. Louis Univ., St. Louis, MO; [3]Biomed. Engin., [2]St. Louis Univ., Saint Louis, MO

Abstract: The ability for the mammalian auditory system to locate sound sources relies on localization cues varying with time, intensity, and frequency. Current generations of hearing aids

do not provide users with comparable performance in localizing and segregating concurrent sources. We have previously developed a robotics algorithm that identifies multiple azimuthal sources in a rapid manner by using a 2D spiral model created at a single sound frequency (Orr et al., Hear Res, 2023). The present study implemented the algorithm in a real-time system, measured its localization errors, and compared the results to human performance obtained under the same conditions. A total of 36 loudspeakers were evenly spaced on a large metal ring, and a dummy head wearing two in-ear microphones was placed at the center to record the single or mixed sound. Once the locations have been determined using our algorithm stored in a computer, the dummy head with a laser pointer fixed at the forehead rotated to face the detected locations. Meanwhile, 15 human subjects were recruited to replace the dummy head and performed the same tasks. In general, humans significantly outperformed (t-test) the robotics system based on a single-frequency model (such as 600 Hz), especially when two or more sounds coexisted. Combining the model across multiple frequencies using a simple machine-learning classifier significantly (t-test) improved the algorithm's performance. Our study sets the foundation for the next-generation hearing aids that can automatically localize and segregate spatial sounds.

Disclosures: E. Flad: None. **R. Gatewood:** None. **O. Adigwe:** None. **I. Gokcen:** None. **Y. Gai:** None.

Poster

PSTR342: Auditory Processing: Sound Localization and Binaural Interactions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR342.15/F17

Topic: D.05. Auditory and Vestibular Systems

Support: Wellcome Trust 227480/Z/23/Z

Title: Mapping auditory space in freely moving ferrets

Authors: *A. P. KHANDHADIA[1], S. M. TOWN[2], S. L. S. DUNN[3], J. K. BIZLEY[4];
[1]Univ. Col. London, London, United Kingdom; [2]UCL Ear Inst., London, United Kingdom; [3]Ear Inst., Univ. Col. London, London, United Kingdom; [4]UCL, London, United Kingdom

Abstract: Natural auditory sensation in mammals must resolve the position and distance of auditory stimuli often during movement. However, many experiments examining spatial responses in auditory cortex often restrain animals and present sounds from limited locations. Experiments that have expanded the number of spatial positions and allowed free-movement have discovered that primary auditory regions can encode sound not only in egocentric, head-centered space but also allocentric, world-centered space (Town, Brimijoin et al. 2017, Amaro, Ferreiro et al. 2021). But these experiments still presented sound from the edges of an enclosure rather than in an immersive soundscape limiting our ability to understand how spatial representations are formed in the auditory pathway. To better understand the structure of world-centered representations, we recorded from ferrets as they freely roamed within a speaker grid

environment. Within this speaker grid, forty individually controlled speakers were located within a 2m by 4m arena, placed beneath an acoustically transparent mesh floor. We recorded from ferrets while presenting click stimuli at intervals of 500-750 milliseconds (ms) from all locations in a pseudorandom sequence while subjects freely explored. Ferrets were previously implanted with 32-channel chronic electrode arrays over primary and some secondary auditory regions of the cortex. While recording, we also captured video and used this footage to train a deep neural network model in Deep Lab Cut (DLC) to track the position of the head, ears, and body of the subjects. From this tracking, we determined the physical position and head angle of the ferret. From the neural recordings, we extracted both local field potentials (LFP) and neural spiking data and aligned both to the timing of clicks from each speaker location. Using the head angle information, we can map the angle of each click relative to the head, and construct head-centered spatial receptive fields, while with the location of each click in the arena, we can construct world centered spatial receptive fields. We will additionally explore how distance, head-pose, and speed influence sound evoked responses. Together this will unlock further understanding about the spatial encoding of auditory stimuli during natural behaviour.

Disclosures: A.P. Khandhadia: None. **S.M. Town:** None. **S.L.S. Dunn:** None. **J.K. Bizley:** None.

Poster

PSTR343: Functions and Dysfunctions in Retinal Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.01/F18

Topic: D.06. Vision

Support: National Natural Science Foundation of China, No. 32070989
National Natural Science Foundation of China, No. 31872766
National Natural Science Foundation of China, No. 81790640

Title: Glucagon-like peptide-1 protects impaired retinal ganglion cells and vision by facilitating presynaptic GABA release in experimental diabetes

Authors: Y.-Q. SHAO[1], Y. WANG[2], L. WANG[1], S.-J. WENG[1], X.-L. YANG[1], ***Y.-M. ZHONG**[1];
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Abstract: Diabetic retinopathy (DR) is a leading cause of blindness in adults. Previous studies have demonstrated that retinal ganglion cells (RGCs) loss is an early event in the pathogenesis of DR that is linked to visual dysfunction or blindness. In the brain, defects in γ-aminobutyric acid (GABA) synaptic transmission are associated with pathophysiological and neurodegenerative disorders, whereas glucagon-like peptide-1 (GLP-1) provides neuroprotection. However, it is not yet clear whether diabetes causes alterations in inhibitory input to RGCs and whether and how

GLP-1 plays a neuroprotective role in diabetic retina by modulating inhibitory synaptic transmission to RGCs. This study used streptozotocin-induced diabetic rats as a model for human type 1-like diabetes mellitus. Using whole-cell patch-clamp techniques, we recorded $GABA_A$ receptor-mediated miniature inhibitory postsynaptic currents (mIPSCs) of RGCs in rat retinal slices. We found that hyperglycemia decreased the frequency of GABAergic mIPSCs of RGCs in streptozotocin-induced 4-week diabetic rats, but had no effect on their amplitudes, indicating a decrease in spontaneous GABA release to RGCs. Topical administration of GLP-1 with eyedrops for 2 weeks prevented hyperglycemia-induced downregulation of GABAergic mIPSC frequency and promoted RGC survival. The protective effects of GLP-1 were eliminated by eyedrops of the specific GLP-1R antagonist exendin-9-39 or the selective $GABA_A$ receptor antagonist SR95531. Moreover, extracellular perfusion of GLP-1 enhanced GABAergic mIPSC frequency in ON- and OFF-type RGCs, which could be mediated by a phosphatidylinositol-phospholipase C/inositol 1,4,5-trisphosphate receptor /Ca^{2+}/protein kinase C signaling pathway, following the activation of GLP-1R. Furthermore, multielectrode array recordings demonstrated that GLP-1 functionally improved the photoresponses of ON-type RGCs. In addition, diabetic rats showed a significant reduction in visual acuity and contrast sensitivity, as determined by optomotor response tests, while topical administration of GLP-1 increased visual acuity and contrast sensitivity in these animals. These findings collectively suggest that GLP-1 facilitates GABA release onto RGCs by GLP-1R activation, which could lead to the de-excitation of RGC circuits, thereby inhibiting the excitotoxic processes in diabetic retinopathy. This study not only enriches our understanding of the protective mechanisms of GLP-1 in the course of DR, but also provides new important clues for the potential transfer of the experimental results to the clinical arena.

Disclosures: Y. Shao: None. **Y. Wang:** None. **L. Wang:** None. **S. Weng:** None. **X. Yang:** None. **Y. Zhong:** None.

Poster

PSTR343: Functions and Dysfunctions in Retinal Circuitry

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Program #/Poster #: PSTR343.02/F19

Topic: D.06. Vision

Support: 1R01EY031663

Title: Single-cell analysis of the epigenome and 3D chromatin architecture in the human retina

Authors: *Y. YUAN[1], N. R. ZEMKE[2], P. BISWAS[6], K. DANG[3], M. WU[3], M. D'ANTONIO[4], Y. XIE[5], Q. YANG[3], K. DONG[3], P. LAU[3], W. BARTOSIK[3], J. BUCHANAN[3], K. WANG[3], S. LEE[3], Z. GIBBS[3], A. WANG[3], S. PREISSL[3], R. AYYAGARI[3], B. REN[3];
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Diego, San Diego, CA; [6]Ophthalmology, Shiley Eye Institute, Univ. of California San Diego, La Jolla, CA

Abstract: Thousands of genetic risk variants for ocular disease have been identified from genome-wide association studies (GWASs), but our understanding of their effects on gene regulation is still limited. Here we investigated the gene-regulatory programs in three human eye tissues including retina, macula, and retinal pigment epithelium (RPE). We profiled gene expression, chromatin accessibility, DNA methylome, and chromosomal conformation profiles at single cell resolution in over 58,000 cells and used the data to determine the epigenome and 3D chromatin organization in 23 distinct retinal cell types. We characterized cell type specific gene expression programs. We carried out a comparative analysis between human and mouse retina, revealing evolutionarily conserved and divergent features in gene-regulatory programs. We employed a sequence-based deep learning predictor of cis-regulatory activity, which demonstrated conservation of the gene regulatory grammar between human and mouse. Linkage disequilibrium score regression (LDSC) identified the relevant cell types and cis-regulatory elements for multiple vision disorders, such as macular telangiectasia and age-related macular degeneration. By integrating our multi-modal data, we annotated non-coding risk variants associated with retina disease and provide insight into how these risk variants promote disease pathology. Our study establishes a retina-wide, single-cell RNA, ATAC, DNA methylome and 3D multi-omics atlas and provides a valuable resource for comprehending the gene regulatory programs of the human retina, generating mechanistic insights into eye disease.

Disclosures: Y. Yuan: None. **N.R. Zemke:** None. **P. Biswas:** None. **K. Dang:** None. **M. Wu:** None. **M. D'Antonio:** None. **Y. Xie:** None. **Q. Yang:** None. **K. Dong:** None. **P. Lau:** None. **W. Bartosik:** None. **J. Buchanan:** None. **K. Wang:** None. **S. Lee:** None. **Z. Gibbs:** None. **A. Wang:** None. **S. Preissl:** None. **R. Ayyagari:** None. **B. Ren:** None.

Poster

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JST PRESTO
R-GIRO

Title: A common mechanism for pathological ganglion cell oscillations in the Trpm1 KO and rd1 mouse retinas

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Abstract: Retinal ON bipolar cells (BCs) express TRPM1, transient receptor potential cation channel subfamily M member 1, which is regulated by metabotropic glutamate receptor subtype 6 (mGluR6). Both *Trpm1* knockout (KO) and *mGluR6* KO mouse retinas are models of congenital stationary night blindness. The outer plexiform layer of both mutant mouse retinas looks normal, but retinal ganglion cells (RGCs) generate spontaneous oscillatory firings (oscillations) not in the *mGluR6* KO but in the *Trpm1* KO mice. The *rd1* mouse, a model for retinitis pigmentosa, also generates RGC oscillations, which are generally considered to be triggered by photoreceptor degeneration. Here, we examined whether properties of RGC oscillations are shared by the *Trpm1* KO and *rd1* mouse retinas. Experiments were performed with 1-2-month-old *Trpm1* KO mice (129 Sv/Ev background) for electrophysiology, and 1-month-old WT and *Trpm1* KO mice (129 Sv/Ev background) and 1-month-old WT, *mGluR6* KO and *rd1* mice (C57BL/6J background) for immunohistochemistry. Applying the whole-cell recording technique to αRGCs, we revealed that oscillations in the *Trpm1* KO mouse retina were similar to those of the *rd1* mouse retina in fundamental frequency (~8 Hz) and phase of oscillations (anti-phase in a pair of ON and OFF αRGC types and in-phase in a pair of the same αRGC types). RGC oscillatory firings were evoked by periodical synaptic currents: EPSCs in ON αRGCs and IPSCs in OFF αRGCs. These synaptic currents were eliminated by blockers specific to the ON and OFF pathways from AII amacrine cell (AII AC) to αRGCs. Our electrophysiological and pharmacological analyses suggest that oscillations in the *Trpm1* KO mouse retina may be generated by AII AC. Next, using immunohistochemistry, we investigated morphological changes in the *Trpm1* KO and *rd1* mouse retinas. We found that the rod bipolar cells (RBCs) in both *Trpm1* KO and *rd1* mouse retinas had shorter and smaller axon terminals than those of WT and *mGluR6* KO mouse retinas. Finally, we constructed a retinal neuronal circuit model, which reflected a loss of ON responses and the shrinkage of RBC axon terminals in the *Trpm1* KO mouse. Model simulations could reproduce RGC oscillations as well as the effects of blockers on RGC oscillations. In conclusion, our analyses suggest that the pathological RGC oscillations may be caused by common retinal mechanisms regardless of photoreceptor degeneration.

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Poster

PSTR343: Functions and Dysfunctions in Retinal Circuitry

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.04/F22

Topic: D.06. Vision

Title: The coding of global visual information by retinal ganglion cells

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Abstract: The retina, the first stage of the visual system, is widely considered to be responsible for transmitting information of filtered image to the brain. The response of individual visual neurons is largely determined by the light information within the classical receptive field. However, it was revealed in cortical visual neurons that features of light stimuli in spatially distant regions far beyond the classical receptive field modulates the response. Previous studies have demonstrated that a specific type of frog retinal ganglion cells (RGCs), known as dimming detectors, is involved in the encoding of large dark objects. Here, we explored non-classical receptive field properties of RGCs in the frog retina. Spike discharges from RGCs were recorded with a multi-electrode array. The center of receptive fields of each cell was identified by the reverse correlation method. The edges of large black-filled object motion triggered the spike discharges when the edge moved far away from the receptive field center. To illustrate this property qualitatively, we calculated the raster plot fixed on the position of receptive field center and overlayed the changing positions of the edge. Spike discharges were observed when the edge moved at the position much larger than the receptive field center or the diameter. Therefore, the underlying mechanism may be associated with widely connected horizontal neural network in the retina. These findings provide new insights into the complexity of neural processing in the retina, and the mechanism of visual information coding by neural circuit.

Disclosures: J. Umemoto: None. **S. Murakami:** None. **H. Ishikane:** None.

Poster

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Topic: D.06. Vision

Support: AMED 21ek0109518h0001
AMED 24ek0109726h0001

Title: Evaluation of the durability of a photoelectric dye-coupled polyethylene film (OUReP) that elicits spike discharges in retinal ganglion cells

Authors: *H. ISHIKANE[1], J. UMEMOTO[1], S. MURAKAMI[1], T. UCHIDA[2], T. MATSUO[3]; [1]Dept. of Psychology, Senshu Univ., Kanagawa, Japan; [2]Grad. Sch. of Environment, Life, Natural Sci. and Technology,, Okayama university, Okayama, Japan; [3]Grad. Sch. of Interdisciplinary Sci. and Engin. in Hlth. Systems, Okayama Univ., Okayama, Japan

Abstract: Various retinal prostheses are under development, with electrode array implants being particularly noteworthy for their ability to stimulate nerves and potentially improve vision in patients with retinitis pigmentosa. The Okayama University-type retinal prosthesis (OUReP) represents a novel approach. It consists of a photoelectric dye-coupled polyethylene film that generates an electrical potential in response to light. Previous studies have confirmed the safety and efficacy of the OUReP as a retinal prosthesis in a monkey model of age-related macular degeneration. In this study, we recorded spikes from retinal ganglion cells to determine whether OUReP could elicit spike discharges in response to light stimuli. Bleached OUReP was also used to evaluate the durability of OUReP. Mice (C57BL/6J) were used for electrophysiological experiments in accordance with the guidelines of Senshu University (#2022-1, #2022-6) and The Physiological Society of Japan. An isolated mouse retina was positioned on OUReP or a plain film within the recording chamber, with the ganglion cell layer facing upwards. All surgical procedures and experiments were conducted in a dark room. The tip of a single conventional tungsten electrode was placed in the ganglion cell layer to record multi-unit activities (MUAs) from retinal ganglion cells Spatially uniform light stimuli were presented onto the retina and films with a LED. L-AP4 was applied to the bath solution to suppress synaptic transmission from photoreceptors to ON bipolar cells. With the plain film, both ON responses and OFF responses were observed when the retina and the film were illuminated by the LED. During the application of L-AP4, ON responses were suppressed. On the other hand, ON responses remained during the application of L-AP4 using OUReP. With bleached OUReP (dye residual rate 23.8%), which corresponds to the percentage of pigment remaining measured after 6 months in an implantation experiment using monkeys, ON responses remained during the application of L-AP4. These results suggest that OUReP could activate retinal neurons, and that the film might be usable for 6 months. OUReP could potentially be utilized as a retinal prosthesis for retinitis pigmentosa and other diseases in which photoreceptor cells are impaired.

Disclosures: H. Ishikane: None. **J. Umemoto:** None. **S. Murakami:** None. **T. Uchida:** None. **T. Matsuo:** None.

Poster

PSTR343: Functions and Dysfunctions in Retinal Circuitry

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CONACYT #664900

BRAIN CANADA FOUNDATION-AZRIELI FOUNDATION
CIHR IRSC

Title: Studying light-evoked retinal responses following optogenetic vision therapy

Authors: *K. ROJAS GARCIA[1], N. ARNOLD[1], E. R. CIANFARANO[1], A. VILLEMAIN[2], S. TRENHOLM[2];
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Abstract: Background & Goal: Retinal degenerative diseases are a leading cause of vision loss and arise from the loss of rods and cones. Following photoreceptor degeneration, other cells in the retina that remain intact could be targeted with optogenetics as a therapeutic strategy. However, the healthy retina sends out many channels of visual information, via different functional types of retinal ganglion cells (RGCs), that each code different features, such as motion, contrast, edge orientation, etc. Due to technical limitations, it may not be possible to restore all of these channels with optogenetics. Our goal is to examine how processing of visual inputs is altered in visual cortex when optogenetic tools are delivered directly to RGCs, reducing the diversity of retinal ganglion cells to a single function type. **Methods:** Experiments are performed in rd1 mice, a model of retinitis pigmentosa who lose vision due to photoreceptor degeneration, and Gnat1/2 mutant mice whose photoreceptors are non-sensitive to light and are a model of congenital blindness. We perform intravitreal injections with AAVs to express MW-opsin specifically in RGCs. To test whether vision has been restored, we screen mice with a light-room/dark-room test and check their retina for fluorescence. To examine light responses of RGCs, we place retinae on a 256-channel multi-electrode array and present the retina with a series of movies. To examine light responses in visual cortex following vision restoration, we perform *in vivo* 2-photon calcium imaging from V1. **Results:** We have successfully expressed MW-opsin in the retina of blind animals and found that their vision is restored when assessed in a light-room/dark-room screen. We have obtained restored light responses from treated rd1 and gnat2/1 retinae and found these responses are all ON-type, with reduced orientation/direction selectivity and reduced diversity in spatial/temporal frequency preferences compared to WT retina. We are currently assessing the impact of such retinal vision restoration on response properties of neurons in V1. **Conclusions:** This work provides the first detailed description of how delivering optogenetics to RGCs in the blind retina collapses the diversity of feature selectivity in the retina and addresses the extent to which visual cortex is able to maintain a diversity of feature selectivity properties. These results will be impactful for development of future vision restoration approaches as they provide critical insights into the extent to which visual cortex can compensate for non-normal restored retinal responses.

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Poster

PSTR343: Functions and Dysfunctions in Retinal Circuitry

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Program #/Poster #: PSTR343.07/F25

Topic: D.06. Vision

Title: Subtypes of dimming detectors in bullfrog's retina

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Abstract: Frog's retinal ganglion cells (RGCs) are generally classified into four main types: the contrast detector, the convexity detector, the moving-edge detector, and the dimming detector (Lettvin et al., 1959). This research aimed to subdivide dimming detectors into subtypes of dimming detectors based on responses to light stimuli. This research focused on how the relationship between light stimuli and adaptation level contributed to responses. The bullfrog's retina was isolated and placed onto a multi-electrode array (MEA) to record spike discharges from RGCs. All light stimuli were spatially uniform, and their intensity was temporally modulated in this research. The sinusoidally modulated light stimuli were used to identify dimming detectors. Only dimming detectors showed sustained responses to the off phase of the light stimuli. Next, the retina was exposed to the background light (the adaptation level). The single trial of the test stimuli consisted of positive and negative flashes with a specified interval. The absolute value of the difference in light intensity from the adaptation level was equal in both cases. Recorded spike discharges were sorted for each RGC and a peri-stimulus time histogram (PSTH) was calculated from responses to the test stimuli. We found that dimming detectors were subdivided into distinct two groups. The first type of dimming detectors was activated in the off phase of both the positive and negative flash. The second type of dimming detectors was activated only by the negative flash in the off phase. Both types of dimming detectors are basically OFF ganglion cells, though the latter of the dimming detectors responded only when the intensity of the light stimulus was reduced below the adaptation level. These results indicate the existence of two subtypes of dimming detectors. It has been demonstrated that dimming detectors were involved in escape behaviors of bullfrogs (Ishikane et al., 2005). Our results suggest that these two types of dimming detectors function in parallel to regulate escape behavior.

Disclosures: S. Murakami: None. **J. Umemoto:** None. **H. Ishikane:** None.

Poster

PSTR343: Functions and Dysfunctions in Retinal Circuitry

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Topic: D.06. Vision

Support: NSF IOS-2129683
Cystic Fibrosis Foundation

Title: Neuronal CFTR interactions and implications for synaptic transmission.

Authors: *B. LEVISKAS, P. K. WALL, E. L. GLEASON;
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Abstract: The function of the cystic fibrosis transmembrane conductance regulator (CFTR) is well established in the context of epithelial tissue due to the debilitating effects of mutations that cause the disease cystic fibrosis. In our lab, a role for CFTR has been established in the regulation of cytosolic Cl^- in retinal amacrine cells (ACs) (Krishnan *et al.*, 2017). Here we ask if there are specific interactions between CFTR and synaptic proteins. Co-Immunoprecipitation (Co-IP) experiments demonstrate that the synaptic proteins Syntaxin-1A (STX1A) and SNAP-25 bind CFTR. These interactions are further supported by a binding assay that demonstrates an increase in STX1A and SNAP-25 from adult chicken brain derived Co-IP samples that have been supplemented with additional purified recombinant CFTR protein (0.63 μg/mL, 1.26 μg/mL). To further characterize the CFTR interactome in neurons, adult chicken brain Co-IP samples were analyzed via mass spectrometry and the resulting peptide information was processed in Proteome Discoverer (Thermofisher). Resulting interactors were ranked using the Sequest score and the interactome was visualized using Cytoscape with network interactions displayed from StringDB. A total of 520 unique proteins with >70 proteins linked to synaptic transmission were identified. We then asked if CFTR is associated with synaptic or other neuronal structures in the transmission electron microscope (TEM). Adult chicken retinal sections were processed with post-embedding immunogold labeling with a polyclonal CFTR antibody (Abcam). CFTR labeling was found on synaptic vesicles in the inner plexiform layer (IPL) and near active zones, in the outer plexiform layer and IPL. Labeling against CFTR was also found on the ellipsoid mitochondria of photoreceptors. To begin to understand the synaptic function of CFTR in ACs, we asked whether CFTR inhibition effects synaptic function by making whole cell voltage clamp recordings of spontaneous postsynaptic quantal currents from embryonic equivalent day 18-21 ACs with ≥3 presynaptic ACs. Pharmacological inhibition of CFTR with CFTRinh172 (10 μM) increases the frequency of events as compared to control [control, 68.2 ± 20.6 (mean ± SEM, n =5) CFTRinh172, 99.6 ± 25.9, (mean ± SEM, n =5, p =0.003) and wash 81 ± 24.1 mean ± SEM, n =5, p =0.02)], suggesting that CFTR might limit the rate of spontaneous vesicle fusion. Together these data suggest that CFTR plays a role in synaptic function. Future exploration of the neuronal interactome will likely reveal further roles for CFTR in neurons.

Disclosures: B. Leviskas: None. **P.K. Wall:** None. **E.L. Gleason:** None.

Poster

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Support: CIHR project grant
NSERC discovery grant

Title: Cadherin 4 assembles a family of color-selective retinal circuits that respond to light offset

Authors: *A. RANGEL OLGUIN[1], P.-L. ROCHON[1], C. THERIAULT[2], T. W. BROWN[3], M. CAYOUETTE[4], E. P. COOK[1], A. KRISHNASWAMY[1];
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Abstract: Retinal interneurons and projection neurons (retinal ganglion cells, RGCs) connect in specific combinations in a specialized neuropil called the inner plexiform layer (IPL). The IPL is divided into multiple sublaminae, with neurites of each neuronal type confined to one or a few layers. This laminar specificity is a major determinant of circuit specificity and circuit function. Using a combination of approaches we show that RGCs targeting IPL sublamina 1 and 3a express the adhesion molecule cadherin 4 (Cdh4). Using calcium imaging and iterative immunostaining, we classified Cdh4-RGCs into 9 types that each encode unique aspects of dark visual stimuli. Cdh4 loss selectively disrupted the layer-targeting of these RGCs, reduced their synaptic inputs from interneurons, and severely altered their visual responses. Overexpression of Cdh4 in other retinal neurons directed their neurites to s1-3a through homophilic interactions. Taken together, these results demonstrate that Cdh4 is a novel layer targeting system for nearly a third of all RGC.

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Poster

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Topic: D.06. Vision

Title: Use of fluorescent immunohistochemistry and confocal microscopy to visualize serotonin in crayfish retina

Authors: *S. Y. ABBAS, M. E. JACKSON;
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Abstract: Serotonin is widely distributed among vertebrate and invertebrate species, playing a vital role in regulating both behavior and physiological functions. In humans, serotonin governs various activities such as behavior, mood, memory, and gastrointestinal homeostasis. Similarly, in crayfish, serotonin is implicated in anxiety-like behavior, aggression, and social dominance. In this investigation, we employed a primary antibody directed against serotonin to explore its

expression patterns within the crayfish (Faxonius virilis) retina. Following tissue processing and immunohistochemistry labeling, the crayfish retinas were mounted on slides and examined using a confocal microscope. Our results show significant serotonin immunoreactivity in specific areas, including the lamina ganglionaris, medulla externalis, basement membrane, as well as in the soma and axon terminals of retinula cells. Control tissues lacking primary antibodies showed no immunoreactivity. Identifying serotonin immunoreactivity is a crucial step in conducting behavioral studies that explore the dynamics of serotonin.

Disclosures: S.Y. Abbas: None. **M.E. Jackson:** None.

Poster

PSTR343: Functions and Dysfunctions in Retinal Circuitry

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National Science Center, Poland Grant No 2022/47/B/NZ5/03023

Title: Visually evoked retinal responses in a pharmacological model of an early stage of photoreceptor degeneration

Authors: B. BALAMUT[1], P. WEGRZYN[2], H. FERNANDES[2], *A. T. FOIK[3];
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Abstract: While mice models of Retinitis pigmentosa, such as Rho^{P23H} or $PDE6^{rd1-J}$ offer insights into rapidly degenerated retinas, the precise observation of the retinal physiology at different levels of degeneration remains challenging. To investigate electrophysiological changes in the retinal ganglion cells (RGCs) responses, we used sildenafil, an inhibitor of the phosphodiesterase 6 (PDE6), a protein crucial to the phototransduction cascade. Sildenafil significantly reduces visual responses, which resembles degeneration. This study used *ex vivo* retinal recordings from the C57/BL6 mouse strain aged between 1 and 3 months. We recorded retinal ganglion cell (RGC) spikes and electroretinograms (ERG) using multi-electrode arrays during the experiments. To evaluate alterations in response patterns, we projected various patterns (flash/drifting gratings/white noise) onto the photoreceptor layer using an LCD screen and custom-built optics. Recordings were conducted both before and after the addition of sildenafil to induce an abnormal 'degenerated-like' condition. Initially, we manually assigned each RGC to a response type group, for example, ON cell or ON-OFF cells, which enabled the comparison of changes in their behavior after sildenafil treatment. The sildenafil application

attenuated the A-wave and caused a time shift in B-wave ERG signals. These results were also visible on the level of single RGC latency changes. Cell firing patterns of cells are similar to those seen in degenerated mice. The characteristics of RGCs also changed with ON-OFF cells transitioning to an ON firing pattern, indicating the disappearance of certain response components and inactivation of individual pathways. Response latencies increased across all cells, indicating extended temporal and spatial summation time due to a lower number of functioning photoreceptors. Moreover, inhibiting the photoreceptors alters RGC's spatiotemporal receptive field properties by changing preferred parameters of spatial frequency, temporal frequency, size, and orientation stimuli. In this pharmacological model, we can test responses of the same RGCs and the entire retina in healthy and abnormal conditions, which is impossible in the *in vivo* model. Establishing a controlled model allows decoding of how the retina adapts to a decrease of input signals, potentially facilitating initial testing of therapies and drugs in a shorter timeframe than using degenerated retinas from mice. However, it's important to note limitations, such as the inability of our proposed model to mimic circuitry degeneration and negative plasticity observed in a disease.

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Poster

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Topic: D.06. Vision

Support: NIH R01 EY017836-16
Visiting Graduate Fellows in Neuroscience Program

Title: The Role of PACAP in Retinorecipient Circuits

Authors: *K. PIZANO[1], B. N. MATHUR[3], J. H. SINGER[2];
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Abstract: In the retina, pituitary adenylyl cyclase-activating peptide (PACAP) is highly expressed in intrinsically photosensitive retinal ganglion cells (ipRGCs). These ipRGCs transmit light information to several brain regions, including the suprachiasmatic nucleus (SCN) and perihabenular region (PHb). These two areas regulate circadian rhythms and mood, respectively, and are unique in that they receive retinal input exclusively from ipRGCs. In the SCN, genetic knockout (KO) of PACAP is associated with dysfunctions in circadian photoentrainment. However, it is unclear how PACAP modulates ipRGC glutamatergic transmission to alter synaptic functions within this circuit. Likewise, the PHb also contains PACAP-positive ipRGCs fibers, suggesting a potential role for the neuropeptide in mood-related behaviors. In looking at the SCN, our results show that PACAP KOs have deficits in short-term synaptic plasticity,

including decreases in synaptic facilitation, compared to controls. We also show that knocking out PACAP increases the presynaptic release probability in these glutamatergic synapses. In addition, using a corticotropin-releasing factor receptor 1(Crfr1)-GFP mouse line, we demonstrate that PACAP selectively attenuates excitatory synaptic transmission in Crfr1+ neurons, underscoring how PACAPergic modulation can occur in a cell-type-specific manner. These retinorecipient Crfr1+ neurons likely represent a subpopulation of SCN neurons that express VIP, GRP, and the PAC1 receptor (Adcyap1r1) postsynaptically. Lastly, in the PHb, we found that conditional knockout of PACAP in mature ipRGCs alleviates the depressive-like behavior characteristic of mice exposed to irregular light cycles. This suggests PACAP may be a presynaptic regulator of transmission from ipRGCs, possibly allowing ipRGCs to better adapt to long-term stimuli and circadian changes. Taken together, these studies highlight the differential effects of PACAP on retinorecipient populations.

Disclosures: K. Pizano: None. **B.N. Mathur:** None. **J.H. Singer:** None.

Poster

PSTR343: Functions and Dysfunctions in Retinal Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.13/F31

Topic: D.06. Vision

Support: National Institutes of Health grants

Title: Emergence of tuning properties of the pupillary light and contrast responses in the retina and olivary pretectal nucleus

Authors: *X. SONG[1], M. FITZPATRICK[2], D. KERSCHENSTEINER[3];
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Abstract: The pupil responds to luminance (PLR) and contrast (PCoR). Pupil constriction reduces brightness and increases contrast in the retinal image to enhance acuity. Where and how the characteristic luminance tuning of the PLR and the spatiotemporal contrast tuning of the PCoR arise is incompletely understood. Recent evidence (Fitzpatrick et al., Neuron, 2024) indicates that the PLR and PCoR share a retinal pathway. In this pathway, rod signals are transmitted via the primary pathway to type 6 bipolar cells, which provide synaptic excitation to M1 intrinsically photosensitive retinal ganglion cells (M1 ipRGCs). M1 ipRGCs innervate diverse brain areas including the olivary pretectal nucleus (OPN), which mediates pupil responses. Here, we compare responses of M1 ipRGCs, OPN neurons, and the pupil to an array of luminance and contrast stimuli to understand where and how the characteristic tuning of the PLR and PCoR emerge and how luminance and contrast interact to control the pupil and optimize the retinal image for encoding, behavior, and perception.

Disclosures: X. Song: None. **M. Fitzpatrick:** None. **D. Kerschensteiner:** None.

Poster

PSTR343: Functions and Dysfunctions in Retinal Circuitry

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR343.14/F32

Topic: D.06. Vision

Support: Research to Prevent Blindness Grant
University of Rochester Undergraduate Discover Grant

Title: Expression of receptor tyrosine kinases in the ganglion cells of degenerated retinas

Authors: *A. K. ABRAHAM[1,2], L. AFRIMA[1], M. TELIAS[1,3];
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Abstract: In photoreceptor (PR) dystrophies, the irreversible death of rods and cones in the outer retina leaves the surviving inner retina as the only substrate for vision restoration. Since every vision restoration method in PR loss relies on the continued communication between the retina and the brain via the optic nerve - the axons of retinal ganglion cells (RGCs) - understanding whether and how RGCs survive such degeneration is crucial to the field. Currently, there exists conflicting evidence regarding if and how RGCs survive PR death, with some studies suggesting survival of RGCs in late stages of degeneration and some suggesting the death of a sub-population of RGCs. We hypothesize that PR degeneration triggers the activation of a neurotrophic mechanism that promotes RGC survival. Previous studies have highlighted receptor tyrosine kinases (RTKs) as a class of receptors which bind neurotrophic growth factors (NTs), leading to the activation of downstream survival signals. Here, we studied the expression of several RTKs in the inner retina of mice with inherited retinal degeneration. The expression of six RTKs was tested in both wildtype mice with no retinal disease and retinal degeneration mice (rd1, Pde6$\beta^{rd1/rd1}$). Transcriptional status of RTKs and associated NTs was measured in mouse retinal lysates via mRNA reverse-transcription and subsequent quantitative real-time PCR. RTKs of interest were further tested for retinal layer-specific protein expression via immunohistochemistry. Our data shows that PR degeneration in the rd1 retina leads to the upregulation of tropomyosin receptor kinase B (TrkB), colony-stimulating factor 1 receptor, and ret proto-oncogene, with TrkB exhibiting the largest fold-change increase in expression. Additionally, only TrkB shows upregulation relative to RBPMS and Brn3a, two known RGC markers. TrkA and TrkC show overall retinal upregulation, but no change in expression relative to RBPMS and Brn3a. Analysis of various NTs shows downregulation of brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) relative to RBPMS. In addition, immunohistochemical analysis of TrkB localization indicates greater upregulation in the ganglion cell layer of the rd1 retina. Our results suggest the possibility of TrkB upregulation in

the rd1 retina contributing to the RGC survival response. Moreover, the downregulation of BDNF and NGF, previously identified in various ocular dystrophies characterized by RGC degeneration, may indicate the presence of a degeneration dependent neuronal survival mechanism. This constitutes a new survival mechanism previously unknown and potentially crucial for vision restoration.

Disclosures: A.K. Abraham: None. **L. Afrima:** None. **M. Telias:** None.

Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.01/F33

Topic: D.06. Vision

Support: U01NS122040
5P20GM103436

Title: Ultrastructure and synaptic properties of projections to the centrolateral nucleus of the thalamus originating from Pitx2 neurons of the superior colliculus

Authors: *N. NAEEM[1], S. P. MASTERSON[2], A. S. SLUSARCZYK[3], M. E. BICKFORD[4]; [1]Univ. of Louisville, Louisville, KY; [2]Anatom. Sci. and Neurobio., Univ. of Louisville, Louisville, KY; [3]Anatom. Sci. & Neurobio., Univ. of Louisville, Louisville, KY; [4]Anatom. Sci. and Neurobio., Univ. of Louisville Sch. of Med., Louisville, KY

Abstract: Corollary discharge (CD), an internal copy of motor command signals, is thought to be critical for distinguishing external from self-generated sensory signals. Premotor neurons in the superior colliculus (SC) which innervate the brainstem and spinal cord via the predorsal bundle (PDB) send collateral projections to the thalamus (Bickford and Hall, 1989), and inactivation of these projections impairs the ability to predict impending eye movements (Sommer and Wurtz, 2002). The ascending collateral projections of PDB cells are labeled in the Ptix2-Cre mouse line, in which PDB cells of the SC contain Cre-recombinase (Masullo and Mariotti et al., 2019). We took advantage of this line (generously donated by James F Martin, Baylor College of Medicine) to examine the thalamic projections of PDB cells, which include the parafascicular (PF), ventromedial (VM), and centrolateral (CL) nuclei. Virus injections (AAV-ChR2-EYFP) in the primary motor cortex (M1) labeled projections to all PDB cell thalamic targets as well as the deep layers of the SC where the PDB cells reside, providing further evidence of the close association between M1 and the motor layers of the SC. To investigate the synaptic properties of Ptix2 ascending projections, we focused on the CL nucleus. Virus injections (AAV-Ef1a-DIO-dAPEX2) in the deep layers of the SC in Pitx2-Cre mice were used to express peroxidase in a Cre-dependent manner in the Pitx2 neurons and their projections. Ultrastructure analysis revealed that Pitx2 synaptic terminals were the largest terminal type in the CL (1.00 $\mu m^2 \pm 0.58$, n = 264). To examine the synaptic properties of Pitx2-CL terminals, virus

injections (AAV-DIO-ChR2-EYFP) in the deep layers of the SC in Pitx2-Cre mice were used to express Channelrhodopsin in Pitx2 neurons and their projections. In slices maintained *in vitro*, whole cell patch clamp recordings were obtained from CL neurons and Pitx2 terminals were photoactivated. In the majority of recorded CL neurons (71 of 120), activation of Ptix2 terminals using 1 ms pulses of blue light resulted in large amplitude excitatory postsynaptic currents (EPSCs) which occasionally elicited action potentials and were depressed during high frequency photoactivation. Thus, the Pitx2 projections to the CL exhibit both the anatomical and physiological characteristics of "driver-like" thalamic inputs, suggesting that the SC can powerfully impact CL responses. Finally, recorded CL neurons were filled with biocytin. CL neurons extended multipolar dendrites that rarely crossed the borders of the CL into adjacent nuclei. Therefore, the CL forms a discrete thalamic region in which CD signals from the SC can drive activity.

Disclosures: N. Naeem: None. **S.P. Masterson:** None. **A.S. Slusarczyk:** None. **M.E. Bickford:** None.

Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.02/F34

Topic: D.06. Vision

Support: NIH Grant EY035523
NIH Grant P20GM103436
NIH Grant EY031322

Title: Ultrastructure, synaptic properties, and convergence patterns of cortical and pretectal projections to the mouse pulvinar nucleus

Authors: *H. C. BOONE[1], S. P. MASTERSON[1], A. S. SLUSARCZYK[2], M. E. BICKFORD[3]; [1]Anatom. Sci. and Neurobio., Univ. of Louisville, Louisville, KY; [2]Anatom. Sci. & Neurobio., Univ. of Louisville, Louisville, KY; [3]Anatom. Sci. and Neurobio., Univ. of Louisville Sch. of Med., Louisville, KY

Abstract: The pulvinar nucleus (PUL) of the mouse can be divided into a caudal zone that receives its primary or "driving" input from the superior colliculus (SC) and a rostral zone that receives "driving" input from the primary visual cortex (V1; Bennet et al. Neuron, 2019. 102(2): 477-492). We have found that the mouse rostral PUL also receives dense input from parvalbumin-containing (PV) neurons of the pretectum (PT). Thus, we asked whether PUL input from PV-PT neurons exhibits properties comparable to the previously defined "driving" inputs' from V1. We investigated the ultrastructure and synaptic properties of V1 inputs that originate from layer 5 and PV-PT inputs to the rostral PUL, and we examined the degree to which these inputs converge on individual PUL neurons. We administered a cre-dependent adeno-associated

virus (AAV) that selectively induces the expression of dAPEX2 (pAAV-DIO-dAPEX2) in either V1 of RBP4-Cre mice, which express cre-recombinase in layer 5 cortical projection neurons, or in the PT of PV-Cre mice. We found that in the rostral PUL both projections formed large terminals (0.81±0.06 and 0.96±0.06 μm) that contained round vesicles and contacted large caliber (1.08±0.06 and 0.83±0.07 μm) dendrites, anatomical properties associated with 'driving' inputs. We then used optogenetics and in vitro patch clamp recordings to investigate the synaptic properties of PT and V1 inputs to rostral PUL. We administered cre-dependent and non-cre-dependent viruses that induce the expression of Channelrhodopsin-2 (pAAV-hSyn-hChR2(H134R)-EYFP) or ChrimsonR (pAAV-Syn-FLEX-rc[ChrimsonR-tdTomato]), in the PT and V1 of PV-Cre mice . We used an occlusion protocol to independently activate inputs from V1 and/or PT and found that many rostral PUL neurons receive convergent input from both sources. In addition, we found PUL responses to photo activation of PT terminals exhibit frequency-dependent depression, a physiological property associated with "driving" inputs. Finally, we have recorded the activity of PT neurons in awake head-fixed mice that are free to run on a Styrofoam ball and have found that PT neurons exhibit discrete visual receptive fields, and their activity is highly modulated by movement of the mice. Our results suggest that, at least within the visual thalamus, many neurons receive convergent input from two or more "driver-like" inputs so their collective activity may be integrated to form new receptive field properties. Our results further indicate that in the mouse rostral PUL, input from the PT may be used to provide the context needed to distinguish between self-generated and external visual motion (Roth et al., Nature Neurosci 2016 19(2):299-307).

Disclosures: H.C. Boone: None. **S.P. Masterson:** None. **A.S. Slusarczyk:** None. **M.E. Bickford:** None.

Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.03/F35

Topic: D.06. Vision

Support: 5R01EY031322
5P20GM103436

Title: Anatomical organization, synaptic properties, and convergence of tectal and cortical inputs to the mouse pulvinar nucleus

Authors: *J. WHITLEY[1], K. MASON[2], N. NAEEM[2], S. P. MASTERSON[2], A. S. SLUSARCZYK[2], M. E. BICKFORD[2];
[1]Univ. of Louisville Sch. of Med., Louisville, KY; [2]Anatom. Sci. and Neurobio., Univ. of Louisville Sch. of Med., Louisville, KY

Abstract: In the primary visual system, unique classes of retinal ganglion cells target segregated regions of the dorsal lateral geniculate nucleus forming discrete pathways to cortex. The degree to which a similar parallel pathway organization is present in the secondary visual system, which links the retina to cortex via the superior colliculus (SC) and pulvinar (PUL), remains unknown. In mice that express cre recombinase in wide field vertical (WFV) cells of the SC (Ntsr1-GN209-cre, "WFV-cre"), we placed dual cre-dependent virus injections in the SC to examine the topography of WFV-PUL projections; this defined a caudal medial region (Pcm) receiving bilateral nontopographic WFV input and a lateral region (Pl) receiving ipsilateral topographic WFV input. To compare ipsilateral and contralateral WFV-PUL terminals to those originating from the cortex, we placed cre-dependent virus injections in the SC of "WFV-cre" and the cortex of RPB4-cre ("layer 5-cre") or Ntsr1-GN220 ("layer 6-cre") mice to label synaptic terminals with peroxidase. Electron microscopy revealed that terminals arising from ipsilateral WFV cells and cortical layer 5 cells were similar in size and both were significantly larger than terminals arising from contralateral WFV cells or layer 6 cortical cells. To examine the synaptic properties of these 4 types of input, we used viral injections or reporter lines to express channelrhodopsin (ChR2) in WFV, layer 5 or layer 6 cells and photoactivated opsin-expressing terminals while recording from Pcm or Pl neurons in slices maintained *in vitro*. High frequency photoactivation of layer 5 cortical terminals resulted a depression of PUL responses, high frequency activation of layer 6 cortical terminals facilitated PUL responses, and high frequency activation of ipsilateral or contralateral WFV terminals resulted in a mix of facilitation and depression. To examine the potential convergence of these inputs, we employed dual-opsin *in vitro* optogenetics using ChR2 (activated by blue light) and Chrimson (activated by red light) and an "occlusion procedure" to separate responses activated by blue or red light. By photoactivating ipsilateral WFV inputs, contralateral WFV inputs and/or layer 5 or layer 6 cortical inputs, we found a high degree of convergence of all 4 types of input on individual PUL neurons in both the Pcm and Pl. Our results reveal that individual PUL neurons integrate both cortical and subcortical inputs and are heterogeneously organized across the anatomically defined PUL sub-regions. Thus, the secondary visual system does not contain discrete parallel pathways but favors the integration of convergent synaptic input from multiple brain regions.

Disclosures: J. Whitley: None. **K. Mason:** None. **N. Naeem:** None. **S.P. Masterson:** None. **A.S. Slusarczyk:** None. **M.E. Bickford:** None.

Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.04/F36

Topic: D.06. Vision

Support: 1UF1NS122040
3UF1NS122040S1
5P20GM103436
5R01EY031322

Title: Synaptic properties of parabigeminal nucleus projections to widefield vertical cells of the superior colliculus

Authors: *K. C. MASON[1], S. P. MASTERSON[1], K. L. WHYLAND[2], A. S. SLUSARCZYK[1], M. E. BICKFORD[1];
[1]Univ. of Louisville, Louisville, KY; [2]UCLA, Los Angeles, CA

Abstract: The superficial (retinorecipient) layers of the mammalian superior colliculus (SC) send ascending projections to the thalamus and are reciprocally connected to the midbrain parabigeminal nucleus (PBG). Anatomical studies of the chicken tectum (SC homologue; González-Cabrera et al., JCN 2015) demonstrated that the nucleus isthmi (PBG homologue) innervates widefield tectal ganglion cells that project to the nucleus rotundus (pulvinar nucleus homologue). To determine whether these connections also exist in mammals, we took advantage of the NTSR1-GN209 mouse line which contains Cre-recombinase in both PBG neurons and wide field vertical (WFV) neurons that project to the pulvinar nucleus. To examine the ultrastructure of PBG projections, we placed virus injections (AAV-Ef1a-DIO-dAPEX2) in the PBG of NTSR1-GN209 mice to express peroxidase in a Cre-dependent manner. Tissue containing peroxidase-labeled PBG terminals was prepared for electron microscopy and sections were additionally stained with an antibody against gamma amino butyric acid (GABA) tagged to gold particles. We found that PBG terminals are densely packed with synaptic vesicles and form asymmetric synapses with nonGABAergic SC dendrites. Next, we used NTSR1-GN209 mice crossed with a green fluorescent protein (GFP) reporter line (Ai3) and placed virus injections (AAV-DIO-Chrimson-TdTomato) in the PBG to express the channelrhodopsin variant Chrimson and the red fluorescent protein TdTomato in PBG terminals. In slices of the SC maintained *in vitro*, whole cell patch clamp recordings were obtained from GFP-labeled WFV cells and PBG terminals were photoactivated with 1ms blue light pulses at 1-50Hz. PBG neurons and their projections to the superficial SC contain choline acetyl transferase and the type 2 vesicular glutamate transporter (Steinkellner et al. eNeuro 2019), but do not contain the vesicular acetylcholine transporter (Sokhadze et al., JCN 2022). Therefore, it has been unclear whether PBG projections are cholinergic or glutamatergic. We found that photoactivation of PBG terminals elicited excitatory postsynaptic currents in WFV cells that could be blocked by the bath application of AMPA and NMDA glutamate receptor blockers. Therefore, PBG terminals contact WFV cells and release glutamate. The responses of WFV neurons to photoactivation of PBG terminals also exhibited frequency-dependent depression, suggesting that PBG-SC terminals exhibit a high probability of glutamate release. These results indicate that PBG projections to the SC may serve to amplify ascending tectopulvinar signals via glutamatergic synapses on WFV cell dendrites.

Disclosures: K.C. Mason: None. **S.P. Masterson:** None. **K.L. Whyland:** None. **A.S. Slusarczyk:** None. **M.E. Bickford:** None.

Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.05/F37

Topic: D.06. Vision

Support: NSF CAREER 2047298
NIH R34NS111653

Title: Role of parvalbumin-positive (PV+) neurons in modulating visual responses in the mouse superior colliculus

Authors: *A. BANERJEE[1], S. P. MYSORE[2];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: The midbrain sensorimotor hub, superior colliculus (SC), plays a crucial role in a wide range of visually guided adaptive behaviors. Yet, much remains unclear about how different cell types within the SC influence the processing of visual information. In this study, we investigated the role of a specific subtype, namely parvalbumin-positive (PV+) neurons in modulating visual response properties of the excitatory cells in the intermediate layers of the SC (SCi). Using a combination of endoscopic calcium imaging and optogenetics (nVoke miniscope, Inscopix-Bruker and Chromatone multiscope, Neurescence-Bruker), we measured the visual response properties of SCi excitatory neurons (expressing GCaMP6) while activating local PV+ neurons. Contrary to suggestions from previous in vitro brain slice experiments, we demonstrate that in vivo, PV+ neurons in the SCi layers suppress the visual responses of the local excitatory neurons. Mechanistically, this suppression operates as a divisive modulation, revealing how these neurons can contribute to visual processing. The suppressive modulation of local activity by the predominantly GABAergic PV+ neurons in the intermediate SC layers, together with the excitatory, long-range modulation by the predominantly non-GABAergic PV+ neurons in the superficial SC layers, underscores the functional diversity of PV+ neurons in the SC. Additionally, it shows that the PV+ neurons in the SCi may share a common functional role with PV+ neurons in forebrain regions. Our results not only represent a significant methodological advance in the use of calcium imaging to measure sensory responses in the intermediate and deep layers of the SC (with simultaneous optogenetic perturbation), but also shed light on the previously unknown computational rule implemented by a specific neural subtype within the SC.

Disclosures: A. Banerjee: None. **S.P. Mysore:** None.

Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.06/G1

Topic: D.06. Vision

Support: NIH Grant U01NS120820

Title: Retinal ganglion cell input to superior colliculus encodes salient information

Authors: *K. BORGES[1], Y. LIANG[2], R. LU[3], N. JI[4];
[1]Univ. of California Berkeley, Berkeley, CA; [2]Univ. of Maryland Sch. of Med., Baltimore, MD; [3]Janelia Res. Campus, Ashburn, VA; [4]Physics and MCB, Univ. of California, Berkeley, Berkeley, CA

Abstract: The superior colliculus (SC) is critical in detecting and responding to salient stimuli. However, it is unknown whether salience signals are inherited from external sources such as retina and cortex, or arise from the intrinsic circuitry within SC. We used in vivo 2-photon calcium imaging with adaptive optics to examine the activity of retinal ganglion cell (RGC) axon terminals in superficial SC. We found that RGC boutons exhibit similar saliency-related responses to those of SC neurons. Furthermore, most boutons can change their orientation selectivity in order to facilitate saliency detection. Our results show that the tuning of RGCs is highly flexible, and that saliency encoding originates in the retina rather than the SC.

Disclosures: K. Borges: None. **Y. Liang:** None. **R. Lu:** None. **N. Ji:** None.

Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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Topic: D.06. Vision

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NSERC (RGPIN-2019-06479)
CIHR (Project Grant 437007)
Connaught New Researcher Awards

Title: A functionally specific subcortical pathway underlies the modulation of visual processing by contextual global motion

Authors: *X. CHOU[1], M. RUSSO[1], Y. HE[1], L. DE VILLA[1], B. LIU[2];
[1]Univ. of Toronto, Mississauga, Mississauga, ON, Canada; [2]Biol., Univ. of Toronto Mississauga, Mississauga, ON, Canada

Abstract: Our perception of objects can be flexibly affected by their contexts, which helps us to deal with the challenges coming from dynamically changing environments and ethological needs. In the visual system, one most common context is moving backgrounds, which happens when our body or the environment moves. This background motion can powerfully influence the perception of foreground stimuli and the resulting behaviors. Previous studies have mainly focused on the role of cortical circuits in this motional modulation. However, the potential contribution of subcortical circuits remains elusive. Here, we demonstrated that a subcortical

inhibitory circuit plays an essential role in the modulation of brainstem visual processing by background motion. We found that background motion impaired the performance of a visually guided task which requires the proper function of the superior colliculus (SC), a subcortical structure essential for visual perception and behaviors. Correspondingly, background motion also suppressed the SC responses evoked by a local flash. To understand the circuit mechanisms underlying the above phenomena of motional modulation, we applied a combination of methods including neural tracing, electrophysiology and optogenetics. We found that SC received prominent inhibition from the nucleus of optic tract (NOT), and this projection uniquely preferred large gratings moving in the temporo-nasal direction. Next, we showed that silencing the inhibitory NOT-SC projection alleviated the suppression of flash evoked SC activity when large gratings move temporo-nasally. Last, we found that consistent with the effect of silencing NOT-SC projection on SC activity, silencing this pathway partially rescued the visually guided behaviors which is impaired by background motion. Overall, our findings demonstrate that the inhibitory NOT-SC pathway specifically conducts signals encoding global motion to SC, and by doing so it suppresses visual processing of subcortical circuits. Given that inhibitory projections commonly exist between subcortical structures, the mechanism revealed in this study may represent a general principle behind contextual modulation across various sensory modalities.

Disclosures: X. Chou: None. **M. Russo:** None. **Y. He:** None. **L. De Villa:** None. **B. Liu:** None.

Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.08/G3

Topic: D.06. Vision

Support: NIH Grant R01EY026286
NIH Grant UF1NS122040

Title: Vector summation and Bayesian inference of motion direction estimation in the superior colliculus

Authors: *C. LI[1], V. DEPIERO[2], H. CHEN[2], S. TANABE[1], J. CANG[2,3];
[1]Dept. of Psychology, Univ. of Virginia, Charlottesville, VA; [2]Dept. of Biol., Univ. of Virginia, Charlottesville, VA; [3]Department of Psychology, University of Virginia, Charlottesville, VA

Abstract: Visual motion is a crucial cue for the brain to track objects and take appropriate actions, enabling effective interactions with the environment. The predominant model system for studying the transformation of visual motion signals has been the geniculocortical pathway. Our goal in this study is to investigate whether a similar transformation takes place in the retinocollicular pathway. We study how mouse SC neurons integrate motion information using plaids which consist of 2 superimposed drifting gratings of different orientations. The two component gratings of each plaid had the same spatial frequency but a temporal frequency ratio

of 1:4, and their moving directions were separated by 20, 45, 135, or 160 degrees. In response to 20-, 45-, and 160-degree plaids, SC neurons displayed responses consistent with the vector summation (VS) rule which computes the sum of the 2 component gratings' motion vectors. In contrast, neural responses to 135-degree plaids were more similar to the intersection-of-constraints (IOC) prediction, which finds the intersection of the constraints defined by the set of all possible physical motions that share the identical grating motion. We then show that these seemingly contradictary experimental results can be explained by a Bayesian computation in which SC neurons represent a posterior distribution of the plaid direction by combining the VS of grating directions and a prior about the pattern direction based on the constraint of component motion direction. These findings are drastically different from those in the cortex where IOC is the dominant rule when combining inputs from V1 neurons that encode component motion. Our studies thus demonstrate a novel neural computation during motion processing and raise intriguing questions regarding its neuronal implementation and functional significance.

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Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.09/G4

Topic: D.06. Vision

Title: Sound activates a dormant visual-motor pathway bypassing primary visual cortex

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Abstract: Like in other species, the primate visual system is characterized by multiple parallel processing streams, besides the geniculostriate pathway. However, unlike in some of these species, the functional significance of alternative visual pathways remains unknown: increasing evidence suggests that they may be normally completely dormant. We first tested this idea by performing focal, reversible inactivation of the primary visual cortex (V1) and investigating a robust oculomotor phenomenon, called saccadic inhibition. This reflexive phenomenon, which is believed to rely on subcortical eye-movement control circuits (Buonocore and Hafed, 2023), is characterized by an obligatory short-latency cessation of saccade generation after visual stimulus onset, as well as by a concomitant saccade direction biasing, first towards and then away from stimulus location. We reversibly inactivated V1 via muscimol injection, rendering two macaque monkeys cortically blind to a specific visual field location. When we then presented a visual stimulus within this localized scotoma, saccadic inhibition was completely abolished, confirming

a dominance of the geniculostriate pathway, even for this reflexive behavior. Simultaneously recorded superior colliculus (SC) visual responses were additionally diminished. However, why do alternative visual pathways, including direct retinotectal ones, exist at all? We hypothesized that such pathways might still be functional, albeit in a gated manner. During V1 inactivation, we paired a visual onset in the blind field with a sound pulse (50 ms; 1 KHz; suprathreshold) that was completely uninformative about the visual stimulus location. Saccadic inhibition was now partially restored, and it was slightly earlier than when the sound pulse occurred alone. Most importantly, there was a re-emergence of saccade direction biasing towards the visual stimulus location, even though the sound was not spatially informative at all. This direction biasing also persisted even when the sound source location was spatially incongruent with visual stimulus location. These results demonstrate that multi-sensory information can activate an otherwise dormant visual-motor pathway bypassing V1, for example, by gating readout of retinotectal visual signals arriving at the SC. Given the large differences in dominance of geniculostriate versus alternative visual pathways in different animal models, our findings underscore the importance of multi-species comparisons in understanding hierarchical sensorimotor processes, and they inform models of active visually-guided behavior invoking parallel sensory streams.

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Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR344.10/G5

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Title: Conservation and specialization of molecular cell types in mouse, tree shrew, and human superior colliculus

Authors: *Y. LIU[1], J. MCDANIEL[1], L. YANG[1], C. CHEN[1], E. L. SAVIER[2], J. CANG[1], J. CAMPBELL[1];
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Abstract: The superior colliculus (SC) is a crucial sensorimotor center that orchestrates reflexive behaviors and higher cognitive functions, with its superficial layer (sSC) exhibiting a rich array of visual functions. While the layering organization, connectivity, and function of the SC is highly conserved across species, its molecular and cellular evolution is largely unknown. To

bridge this gap, we generated a molecular atlas of mouse and tree shrew sSC cell types through single-nucleus RNA-sequencing and then integrated publicly available human SC transcriptomic data. We clustered the cells by their gene expression profiles across the three species into 31 neuron subtypes, the majority of which are shared by these species, albeit with varying abundance. After classifying neuron subtypes as excitatory or inhibitory based on their gene expression, we found a higher proportion and greater diversity of inhibitory neurons in all species. Notably, we uncovered co-expression of cluster markers and excitatory/inhibitory markers which was generally conserved across species, substantiated by fluorescence RNA in situ hybridization (RNA FISH) in both mouse and tree shrew sSC. On the other hand, our analysis identified species-specific gene expression - e.g., genes which were detected in mouse cells of a consensus cluster but not detected in tree shrew or human cells of the same cluster. Moreover, we detected a unique inhibitory subtype present in the tree shrew and human but absent in mouse sSC. These divergent features and the unique cluster were confirmed by RNA FISH in mouse and tree shrew sSC. Finally, we focused on an excitatory neuron subtype which was the most conserved across species. We demonstrated similar projections from this neuron subtype to the lateral posterior nucleus of the thalamus (the pulvinar) in both mouse and tree shrew. In summary, our study offers a comprehensive resource for understanding the molecular and cellular evolution of the SC. It suggests that the SC has evolved mostly through molecular specialization of conserved neuron subtypes but also by generating a distinct subtype. This resource can also provide a foundation for exploring the evolutionary mechanisms of SC connectivity and function at the cell type level.

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Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

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Title: All Retinal Input to Macaque Superior Colliculus Derives from Branching Axons Projecting to the Lateral Geniculate Nucleus

Authors: Y. J. ZHENG[1], D. L. ADAMS[2], T. N. GENTRY[1], M. D. DILBECK[1], J. R. ECONOMIDES[1], *J. C. HORTON[1];
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Abstract: In primates the superior colliculus receives a direct projection from retinal ganglion cells, partially segregated by eye into alternating columns and layers. It remains unknown if these ganglion cells also supply the lateral geniculate nucleus. This issue was investigated in 2

male macaques. The animals were trained to fixate a target while potential injection sites were scouted in the superior colliculus by recording and stimulating with a tetrode. Once a suitable site was identified, an adjacent micropipette was lowered and cholera toxin subunit B Alexa - Fluor 488 was injected. In a subsequent experiment, cholera toxin subunit B - Alexa Fluor 555 was injected into the lateral geniculate nucleus under general anesthesia at matching retinotopic locations. After a brief survival period, retinal flat-mounts were prepared and a quarter million ganglion cells were examined to determine if they were single- or double-labeled. The ratio varied zone by zone, depending on the relative efficiency of retrograde transport by each tracer and the precision of retinotopic overlap of the injection sites. At locations where these parameters were optimal, every ganglion cell projecting to the superior colliculus was double-labeled. For example, in such a zone measuring 38.9 mm^2, there were 5,746 cells labeled only by CTB-AF555, 561cells double-labeled by CTB-AF555 and CTB-AF488, but no cell labeled only by CTB-AF488. These results indicate that the direct retinal input to the macaque superior colliculus arises from a collateral axonal branch supplied by 3-4% of the ganglion cells that project to the lateral geniculate nucleus. There exist no retinal ganglion cells that project exclusively to the superior colliculus.

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Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

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Topic: D.06. Vision

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Title: Locomotion boosts representations of higher visual speed in retinal axons and neurons within the superficial superior colliculus of mice

Authors: *M. COZAN, L. J. BARUCHIN, S. SCHRÖDER;
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Abstract: Behavioral states have profound effects on sensory processing. Here we investigated how locomotion affects the tuning to spatial and temporal frequency in neurons of the superficial superior colliculus (sSC) and retinal axons projecting to the sSC.
We employed two-photon imaging of calcium activity in retinal axon terminals (boutons) and sSC neurons while mice were head-fixed and able to run on a treadmill. Neural activity was recorded in response to drifting sinusoidal gratings, which varied in their direction of motion, and their temporal and spatial frequency. Behavior in each trial was classified as stationary or running (mean running speed >0.5 cm/s).
We replicated previous findings that running affects the gain and offset of direction tuning

curves in about half of all retinal boutons and sSC neurons. Intriguingly, the impact of running on temporal and spatial frequency tuning could not be explained by additive and multiplicative effects alone. 24% of sSC neurons tuned to temporal frequency changed their preference during running, with ~60% favoring higher temporal frequencies. Of all sSC neurons tuned to spatial frequency, 32% changed their preference during running, with ~60% decreasing their preferred spatial frequency. This is equivalent to higher preferred visual speeds as temporal frequency was kept constant when measuring spatial frequency tuning. Of all tuned retinal boutons, only 10% changed their preference for temporal or spatial frequency with running, but the direction of change was similar to sSC neurons (61% preferred higher temporal frequencies, 64% preferred lower spatial frequencies). The magnitude of shifts was generally larger in sSC neurons compared to retinal boutons, with the largest shifts seen for preferred temporal frequencies, which raised 1.6x in sSC neurons versus 1.3x in retinal boutons.
Together, these findings show that locomotion tends to push neural preferences towards higher temporal frequencies and lower spatial frequencies, both leading to improved representation of higher visual speeds. This modulation takes effect as early as in retinal axons but is further strengthened in sSC neurons receiving retinal input. Early stages of visual processing thus adapt to the visual input statistics experienced during locomotion.

Disclosures: M. Cozan: None. **L.J. Baruchin:** None. **S. Schröder:** None.

Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

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Topic: D.06. Vision

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Title: Cell-type specific connections from the parabigeminal nucleus to the superior colliculus in the mouse

Authors: *A. FORD[1], X. RELOTA[1], E. L. SAVIER[2];
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Abstract: Vision carries ethological relevance to multiple species and enables the coordination of behavioral responses to perceived threat, prey, or relevant environmental and social cues. The superior colliculus (SC) is an important structure within the orchestration of such behaviors and contains canonically defined cell types involved in visual information processing. One of these cell types is the wide field vertical (WFV) cell; which are highly conserved, marked by characteristic morphology, and involved in motion processing. These cells receive inputs from multiple sources and have expansive dendritic arbors and large receptive fields. They project to the lateral posterior nucleus in rodents (the homologue of the pulvinar in primates). Among the regions that provide input to the WFV cells is the parabigeminal nucleus (PBG), a cholinergic,

excitatory structure and a ‘satellite’ region of the SC that has been directly associated with defensive behaviors in rodents. Previous studies have traced the projections from the PBG to the SC, and characterized some of their response properties, but the cell specific targets, as well as the target compartments have yet to be characterized. The SC is retinotopically organized, and regional stimulation of specific parts of the visual field elicit different behavioral outputs. This led us to hypothesize that the PBG to SC connection also shows regional specialization in the mouse. In this study we examine these projection targets using viral vector tracing, immunohistochemistry, and fluorescent in situ hybridization; thus providing evidence towards a functional interpretation of the connections from the PBG to SC, focusing on the WFV cells. So far, our results suggest a specific organization along the dorso-ventral axis of the SC and ipsi-lateral specialization. Together, these results will provide valuable information of the modulatory contributions of the PBG to SC and are a comparative gateway into examining the axis of visual stimulus to behavior in mammals.

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Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

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Title: Synaptic connectivity motifs of horizontal cell dendrites in the tree shrew superficial superior colliculus: a 3D EM connectomics study

Authors: *F. SCIACCOTTA, S. ZHANG, R. ROBERTS, A. ERISIR;
Psychology, Univ. of Virginia, Charlottesville, VA

Abstract: The superior colliculus (SC) is an evolutionarily conserved structure that integrates sensorimotor information to initiate commands for reorienting an organism. This complex function is orchestrated by specific synaptic inputs from multiple excitatory brain nuclei and local inhibitory cells impinging on output neurons, namely the widefield vertical (WFV) cells that project to pulvinar, narrowfield vertical (NFV) cells to the PBG and deep SC, and stellate cells to LGN. Focusing on the intrinsic circuitry that shapes the response properties of output neurons, we examined the synaptic targets and circuitry motifs formed by inhibitory horizontal cell dendrites in the upper SGS of a pre-primate species, the tree shrew. We used a 100um x 100um x 20um image stack prepared for scanning blockface electron microscopy (SBEM), and sparsely reconstructed horizontal cell dendrites as well as their pre- and postsynaptic partners. Almost all horizontal dendrites reconstructed extended over 100 um and formed synapses at periodic intervals onto other vertical dendrites oriented toward the surface. At each node, both horizontal and vertical dendrites receive synapses from an axonal terminal, forming a triad.

Immuno-TEM revealed that some of the excitatory inputs within the triads are retinogeniculate terminals, confirmed by eye injection, and terminals positive for VGluT2 and VGluT1. Some postsynaptic vertical dendrites are smooth and at times ensheathed in extensive astrocytic processes along their entire dorsoventral extent, potentially serving to insulate summated signals or to isolate the dendrite from additional synaptic inputs. Other postsynaptic dendrites displayed thin and beaded morphology, similar to those found at the dorsal tufts of NFV and WFV cells. Both types of dendrites received multiple horizontal dendrite synapses at various depths of the uSGS. As such, horizontal cell dendrites and vertical dendrites form a lattice network, where inhibition can impact the receptive fields of WF or NF vertical cells in a spatial or time-dependent manner. Horizontal cells may also mediate the excitability of other horizontal cells via dendrodendritic synapses at non-triadic zones. Excitatory synapses on horizontal dendrites at non-triadic nodes were sparse. The circuitry motifs observed are consistent with a model that receptive-field specific input excitability is mediated by the triadic arrangement provided by the horizontal cells at every dendritic segment of WFV and NFV cells. Such arrangements may be involved in a focal inhibition mechanism to sharpen the receptive field of the vertical dendrite as an object moves across the field of view.

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Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

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Title: Cellular and synapse-level characterization of the wide field vertical cell circuitry in the tree shrew superior colliculus

Authors: *A. KIPCAK, F. SCIACCOTTA, C. TURNER, R. ROBERTS, A. ERISIR; Psychology, Univ. of Virginia, Charlottesville, VA

Abstract: Superior Colliculus (SC) is a topographically organized midbrain center that help orchestrate visually-guided behaviors. The Wide Field Vertical (WFV) neurons of the SC act as motion detectors and project to Pd and Pc subdivisions of pulvinar nucleus, where two parallel streams (to amygdala and striatum respectively) are thought to arise for defense and pursuit. Previous studies identified unique morphological properties of WFV cells that can differentially contribute to these pulvinar streams however the question of whether there are multiple subtypes of WFV cells with distinct set of inputs and projection targets remain to be answered. To address these questions, we carried out viral tracing experiments coupled to confocal and electron microscopy in a pre-primate species, tree shrew *T. belangeri*. WFV cells filled by retrograde tracer injection into pulvinar (Pd+Pc) are spread across the full lateromedial extent of the lower

SGS (lSGS). Clustering analysis of the labeled soma sizes displayed a bimodal distribution with two populations: WFV cells with big (minority) and small (majority) cell bodies. Cells of both populations are uniformly located in the SGS and project to the ipsilateral pulvinar. Pd-restricted retrograde tracer injection yielded a greater proportion of cells with big cell bodies relative to Pd+Pc case. Furthermore, labeled cells in the lateral extent of the SC were on the bigger end whereas those in the medial SC consisted of both big and small cells. In addition, retinal and cortical inputs innervate the SGS (and WFV dendrites) with an opposing gradient in the dorso-ventral axis: Retinal terminals are the densest in upper dorsal SGS (uSGSd) and sparser in lSGS whereas cortical terminals follow a reverse pattern. Interestingly, confocal and electron microscopy tracing of putative retinal and cortical terminals onto WFV dendrites showed that cortical terminals form dyadic arrangements with retinal terminals on the same dendritic site and that this was most abundant in lSGS where the WFV soma and primary dendritic segments reside. Together, these results suggest that tree shrew WFV cells are likely comprised of two populations with distinct projection targets and synaptic inputs.

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Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

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Title: Task-dependent processing of salient visual stimuli in the macaque superior colliculus and pulvinar

Authors: *A. BERTUCCI[1,2], A. MITOLA[3], C. CAMPANELLO[3,4], L. BONINI[3], M. TAMIETTO[5,6], M. LANZILOTTO[3];
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Abstract: The subcortical visual pathway, involving the superior colliculus (Sc) and pulvinar (Pulv), plays a crucial role in swiftly detecting visual stimuli to adapt behavior and controlling motor outputs. However, it remains unclear whether and to what extent the processing of these stimuli depends on the different behavioral responses and demands, such as detecting them with gaze or manually, or attentively selecting them among multiple options.To tackle this issue, we recorded neurons from the Sc and Pulv of both hemispheres in 2 macaques trained to perform 3 different visuomotor tasks. Visual stimuli belonging to 4 categories (monkey emotional faces, snakes, objects, and monkey bodies) were randomly presented in 4 different locations of the visual field, and animals were required to perform different actions in response to the same stimuli according to the task request. Specifically, in the Detection Task (DT), the monkey had to detect the presence/absence of a peripheral stimulus, regardless of category, by moving a joystick forward/backward, respectively, while maintaining central fixation. In the Forced-Choice Task (FCT), the monkey had to gaze at a predefined peripheral target (emotional faces) while a distractor from the other categories was simultaneously presented. In the Saccade-off Task (SOT), the monkey had to gaze at a peripherally presented stimulus, regardless of category, when the central fixation point disappeared.We isolated a total of 165 neurons, 111 from the Sc and 54 from the Pulv. The majority (over 70%) were responsive in at least one task, displaying mixed combinations of category selectivity and spatial tuning. Stimulus category was encoded by 59% of Sc and 27% of Pulv neurons during SOT, whereas category selectivity significantly decreased during the DT (6% in Sc and 5% in Pulv). When focusing on the emotional faces, which constituted a common visual target for all tasks, as during FCT stimuli from other categories represented a distractor, neurons exhibited similar selectivity during FCT (21% in Sc and 6% in Pulv) and SOT (18% in Sc and 5% in Pulv), but this selectivity decreased markedly during DT in both Sc and Pulv. Moreover, the majority of neurons showing spatial tuning during SOT (52% in Sc, 61% in Pulv) significantly extended their response toward other positions during FCT, while the opposite trend was found in the DT. These findings support the role of these structures in processing salient visual stimuli, based on the effector used and attentional demands, for a flexible adaptation of behavior.

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Poster

PSTR344: Properties of Subcortical Visual Pathways: Superior Colliculus and Others

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Title: Categorical representation of visual stimuli in the macaque subcortical visual pathway

Authors: *C. CAMPANELLO[1,2], A. MITOLA[1], A. BERTUCCI[3], L. BONINI[1], M. LANZILOTTO[1], M. TAMIETTO[3,4];
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Abstract: In addition to the retino-geniculate pathway involved in conscious perception, retinal input is relayed also to the Superior Colliculus (SC) and Pulvinar (Pulv). These structures are crucial for different visuo-motor functions that persist also after damage to the visual cortex, including rapid detection of salient stimuli that may require adaptive response. Specifically, prior studies have shown that SC neurons exhibit faster response times for face-like patterns compared to simple shapes or non-salient stimuli. However, with the exception of a few studies showing evidence of visual selectivity for snakes and faces of conspecifics in SC and Pulv, the individual contribution of these two functionally interconnected areas in the encoding and categorization of complex visual stimuli remains poorly investigated. In our study, we simultaneously recorded neuronal activity in two macaques from distinct bilateral regions of the subcortical visual pathway, SC and Pul, while the monkeys performed a fixation task. Stimuli belonging to seven different categories (human and monkey faces and bodies, foods, objects, and snakes) were presented at five different locations in the visual field (one at the primary position, and four at 45° polar angle and 15° eccentricity). Additionally, two types of control stimuli were used: a scrambled version and a background mask devoid of any content. Preliminary analysis on 87 neurons in the SC and 64 neurons in the Pulv revealed that visual stimuli modulated approximately 41% of SC cells and 47% of Pul cells. Neurons in both Pulv and SC exhibited selectivity either for specific stimulus categories (24% and 25%, respectively) or for the spatial position of stimuli within the visual field (27% and 44%,), with some demonstrating an interaction between these factors (35% and 40%). Notably, the Pulv can discriminate amid stimulus categories better than the SC, as shown with a classifier trained to distinguish stimulus categories based on neural activity in both structures independently. These findings offer valuable insights into how complex visual stimuli can be encoded and categorized by structures in the subcortical visual pathway.

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Poster

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Title: Signaling of the strongest stimulus in multi-stimulus scenes by the optic tectum: Rescue of loss of accuracy in individual neuronal responses by population responses

Authors: *S. MARTIN[1,2], G. T ANANDAN[3], J. HUNTLEY[4,2], S. P. MYSORE[3];
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Abstract: The optic tectum (OT), and specifically, its intermediate and deep layers (OTid), constitute a major multisensory and motor hub in the vertebrate midbrain. It is known to play a critical role in stimulus selection across space and in spatial decision-making. In the barn owl, individual OTid neurons have been shown to signal the strongest (and more generally, the higher priority stimulus) among *two* competing stimuli, accurately as well as categorically. Specifically, responses of OTid neurons to a stimulus inside the receptive field (RF) remain high as long as this stimulus is the stronger one, and the responses drop to a low value just when a competitor outside the RF becomes stronger. Notably, however, as the number of competitors is increased, responses of individual OTid neurons: (a) become weaker, and (b) no longer accurately signal the strongest stimulus. Indeed, individual neurons exhibit a progressive loss of accuracy as the number of competitors is increased. This raises the question of efficacy of OTid signaling for mediating spatial stimulus selection in complex (naturalistic) scenes. Here, we show that the accuracy of signaling the strongest stimulus by the *population* of neurons across the OTid space map remains remarkably accurate (as well as categorical) even with an increasing number of competitors. Moreover, the time course of signaling by the population as well remains largely independent of the number of competitors. We show that this surprising rescue of signaling accuracy by the population is the result of suitably complementary changes in neural responses at the different locations across the space map corresponding to the multiple stimuli. Thus, whereas local signaling in OTid is seemingly compromised in multi-stimulus scenes, ensemble signaling, which very likely underlies downstream decoding and behavioral outcomes, continues to support accurate stimulus selection. Our results shed new light on the neural basis of multi-stimulus selection and decision-making.

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Poster

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Title: Pupillary responses to visually salient stimuli in barn owls

Authors: *G. T ANANDAN[1], S. P. MYSORE[2];
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Abstract: Previous research across multiple species has demonstrated that pupil responses are influenced by stimulus salience. In barn owls, studies have exclusively explored these responses to auditory stimuli, which typically produce pupil dilation of increasing magnitude with auditory signal-to-noise ratio (SnR). However, whether and how pupil responses in barn owls relate to the salience of visual stimuli is not known. Interpreting pupil responses to visual stimuli is complex due to the pupillary light reflex, which induces constriction, in part, to regulate light entry. Recent findings suggest that another function of pupil constriction is to enhance visual processing, particularly visual acuity and sensitivity to spatial frequency, rather than merely regulating light intensity. Here, we investigate the relationship between pupil responses and visually salient stimuli under uniform lighting conditions, separating the impact of salience from light-induced constriction. By comparing responses to global luminance changes, stimulus-specific changes, and isoluminant visual stimuli of varying salience, we aim to elucidate how visual stimulus salience affects pupillary responses. Our results indicate distinct steady-state pupil sizes in response to global luminance changes but not to stimulus-specific changes. They also demonstrate pupillary responses correlated with increasing salience of isoluminant stimuli. This research quantifies how pupil dynamics in barn owls signal important environmental visual cues beyond basic light regulation and prompts the possibility of using pupil responses as a 'behavioral' readout for visual stimulus salience.

Disclosures: G. T Anandan: None. **S.P. Mysore:** None.

Poster

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Title: Features of diencephalic visual relay nuclei-telencephalic projections in a teleost common with mammals

Authors: H. HAGIO[1,2], *N. YAMAMOTO[1];
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Abstract: Recognizing where things are present is important for most vertebrates including fish to survive. Two ascending visual pathways from retina to the telencephalon (cerebral cortex) are

present in them. One of the pathways, in mammals, is called the geniculate system, and the other is called the extrageniculate system. In actinopterygians, cypriniform fishes (such as the goldfish and carp) possess similar two visual pathways, while holocentriform fishes (such as the squirrelfish) and the yellowfin goby have only an extrageniculate-like pathway. We found that the retinal inputs reach mainly the lateral part of the dorsal telencephalon (Dl) via the optic tectum and then the nucleus prethalamicus (PTh) in the diencephalon in goby. We also revealed topographic organization of the retino-tecto-diencephalic visual relay nucleus pathway, as in mammals (Hagio et al., 2021). However, it is unclear in teleosts whether or not positional information is preserved up to the telencephalon.
We investigated diencephalic visual relay nuclei-telencephalic projections by tract-tracing methods in the yellowfin goby. The PTh is composed of two subnuclei (medial [PTh-m] and lateral [PTh-l]) and PTh-l is divided into two regions (PTh-lm and PTh-ll) (Hagio et al., 2021). We revealed that the PTh-m and PTh-lm, which receive information of dorsal visual field, each projects to five regions of the dorsal telencephalon. We also found that PTh-ll, which receives information of ventral visual field, projects to four regions of dorsal telencephalon. Our data show that some regions of dorsal telencephalon receive information of dorsal and ventral visual fields from the PThl-m and PTh-ll, respectively. In one of them, dorsal and ventral zones receive information of dorsal and ventral visual fields, respectively. These results suggest that dorsal and ventral visual fields are represented topographically within a dorsal telencephalic region, while information of the dorsal and ventral visual fields is processed in a mixed fashion. Furthermore, we observed that these visual regions project to other regions of dorsal and ventral telencephalon, suggesting the presence of higher order visual centers in the telencephalon. These features are common to those of mammals.

Disclosures: H. Hagio: None. **N. Yamamoto:** None.

Poster

PSTR345: Visual Motion Perception

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.01/G16

Topic: D.06. Vision

Title: Fixating an eccentric static target causes apparent target motion

Authors: *J. SMEETS[1], M. DI CARLO RIATO[1], Z. G. ÖZTÜRK[2], J. BOS[1,3];
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Abstract: The perception of motion is in general based on a combination of retinal and extraretinal signals. When fixating an object in the dark, only extraretinal signals (efferent and afferent) will contribute to this percept. Both components are ambiguous: they can signal a more eccentric orientation or eccentric motion. Therefore, we predict that viewing a static target eccentrically might induce a percept of that target to move eccentrically. We performed two

experiments using a two-alternative forced-choice paradigm to test whether this illusion (which we will refer to as “eccentric motion illusion”) occurs in healthy participants.
In the first experiment, participants were wearing a VR headset, and subjected to phases of acceleration, deceleration, and constant velocity on a rotating chair. The headset displayed a target in the dark, and the participants had to judge whether this target was moving leftward or rightward with respect to themselves. As expected from the literature, we found clear effect of rotational acceleration (the oculogyral illusion). Most importantly, we found in addition a clear eccentric motion illusion. In a second experiment, the participants were seated in a dark lab, viewing a dark computer screen on which we presented either a single static target (at various eccentricities) or a target that started at an eccentric position and was moving to the center of the screen (with various low velocities) to counteract the illusion if it would occur. Again, we found the eccentric motion illusion. In addition, we found that the illusory motion was proportional to the eccentricity, and the perceived speed (in °/s) was about 1/80 of the eccentricity (in °). We conclude that perceived motion depends systematically on eye orientation.

Disclosures: J. Smeets: None. **M. di Carlo Riato:** None. **Z.G. Öztürk:** None. **J. Bos:** None.

Poster

PSTR345: Visual Motion Perception

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Program #/Poster #: PSTR345.02/G17

Topic: D.06. Vision

Support: F31 EY034016
T32 EY025187
R25 NS117356
DGE 1734815
UMN Grant-in-Aid

Title: The motion aftereffect in visual snow

Authors: *S. MONTOYA[1], A. HILLSTROM[2], K. ALLISON[3], C. MULDER[4], M. S. LEE[5], S. A. ENGEL[6], M.-P. SCHALLMO[7];
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Abstract: Visual snow syndrome (VSS) is a condition where one sees innumerable tiny flickering dots—similar to dynamic noise—covering the entire visual field. VSS can interfere with daily activities like driving and reading, and is estimated to affect about 2% of the

population. The mechanisms underlying VSS are poorly understood, which has limited the development of effective treatments. Our previous work suggests that visual snow arises from spontaneous (non-stimulus driven) activity in the visual pathways, but the specific regions involved are unknown. We sought to constrain those regions by determining whether the visual snow percept is susceptible to visual illusions known to depend upon neurons with specific preferences. Specifically, the motion aftereffect (opposite-direction illusory motion perceived after adapting to motion) is known to depend upon activity in motion selective neurons including global motion processing area medial temporal (MT) cortex. If the activity producing visual snow reaches these neurons, then adapting to motion should cause the visual snow percept to appear to drift in the opposite direction. Ten participants with VSS adapted to high-contrast drifting gratings on the left and right sides of a central fixation point. The gratings (0.3 cyc / degree, 2 Hz) drifted horizontally towards or away from the center. Following adaptation, a blank screen with only the fixation mark was shown. Participants judged the motion of their visual snow, and pressed a button when it matched on both sides, allowing us to measure the duration of the motion aftereffect. The duration of the adapter gratings varied across trials (1.6, 5, 15, or 45 sec, each repeated on 4 trials). In a control condition, we presented a stationary stripe pattern during the test period to assess whether participants with VSS experienced a typical motion aftereffect for external stimuli. Participants with VSS reported that their visual snow flowed in the opposite direction of the adapting gratings. The effect durations showed a typical motion aftereffect for both the stationary test pattern and the visual snow percept, with increasing adapter durations resulting in longer-lasting illusions (ANOVA $F_{9,3} = 14.6$, $p < 0.0001$). The effect was slightly stronger for the stationary pattern than the visual snow (ANOVA $F_{9,1} = 7.3$, $p = 0.024$). Because visual snow was susceptible to the motion aftereffect, it is likely that the neural activity responsible for snow reaches motion selective neurons. Specifically, this suggests neural loci at or before area MT in the visual pathways.

Disclosures: S. Montoya: None. **A. Hillstrom:** None. **K. Allison:** None. **C. Mulder:** None. **M.S. Lee:** None. **S.A. Engel:** None. **M. Schallmo:** None.

Poster

PSTR345: Visual Motion Perception

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.03/G18

Topic: D.06. Vision

Title: Visual motion categorization based on single moving objects

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Abstract: It is critical for animals' surviving to recognize predator and prey as early and far as possible. Thus, for visual animals, they need to be able to detect and distinguish the moving objects with distance, even though the information of their shapes is unavailable.

The objective of the present study is to examine whether non-human primate can learn to distinguish two sets of single moving objects (with identical shapes) that were drawn from videos of flying bird and drone, and eventually to examine whether they are able to correctly categorize novel moving objects. Then, we seek the possible strategies to perform the task and the underlying neural mechanisms. During training phase, for each trial, one of 58 moving single dot (29 for each set) was randomly presented to animals. Two monkeys were trained to categorize them into two different sets only based on the motion characteristics. Neural activity was recorded from titanium screws that were located under skull but above dura. After weeks of training, monkey was able to categorize most of moving objects correctly and when facing novel objects, monkey can still reach high correct rate after a few trials which suggests monkey may use concept learning method instead of memorize the moving patterns (trajectories) for categorization. The eye movement analysis showed monkey didn't always pursuit the whole trajectory of moving object before making decision, which gives us clues that monkey may utilize certain motion feature as evidence. The stepwise linear regression (R2 = 0.86) the acceleration of the moving objects may be the priority evidence for monkey's categorization (Standardized Coefficient = 0.771, p<0.001). Our results shows that monkey could categorize single moving objects only based on motion features and acceleration may play a priority role in this processing.

Disclosures: Z. Zhang: None. **D. Xing:** None. **M. Zhang:** None.

Poster

PSTR345: Visual Motion Perception

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Topic: D.06. Vision

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Title: Distinct effects of electrical microstimulation in macaque areas MT and FST on 3D motion perception

Authors: *Z. ZHU[1], L. W. THOMPSON[3], M. ABDALAZIZ[2], R. DOUDLAH[2], B. KIM[4], A. ROSENBERG[5];
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Abstract: The visual perception of three-dimensional (3D) object motion begins with the processing of a pair of eye-specific patterns of two-dimensional (2D) retinal motion. Recent work found that neurons in the macaque middle temporal (MT) area are predominantly selective for 2D retinal motion. In contrast, the fundus of the superior temporal sulcus (FST) contains similar proportions of neurons with 2D retinal- or 3D motion selectivity. Based on those findings, we proposed a labeled-line model in which the output of MT conveys eye-specific retinal-motion signals that are selectively integrated by downstream neurons to compute a prevalent representation of 3D motion at the level of FST (Thompson et al., 2023; *Cell Reports*). To test this model, here we assess the behavioral effects of applying electrical microstimulation (EM) to 2D or 3D selective neurons located in MT or FST during a 3D motion (toward/away) discrimination task. As predicted by the labeled-line model, the EM of 2D selective MT neurons produced behavioral biases that were determined by an interaction between the preferred retinal-motion direction and ocular dominance at the stimulation site. In contrast, the EM of 2D selective FST neurons elicited little-to-no behavioral effect. Importantly, this cross-area difference in the effects of EM were not explained by the magnitude of ocular dominance of the stimulated neurons or the clustering of visual feature selectivity. These results suggest that the output of 2D retinal-motion selective neurons in MT, but not FST, subserve downstream 3D motion computations. In contrast, the EM of 3D selective FST neurons induced behavioral biases that were determined by their 3D direction preferences, implying a more direct contribution to 3D motion perception. Similar results were observed during the EM of 3D selective MT neurons, but such neurons were rarely observed. These results collectively suggest different computational roles for MT and FST in visual motion processing. Namely, that MT predominantly carries information about eye-specific retinal-motion velocities and that the selective integration of this output yields a downstream representation of both 2D and 3D motion directions in FST.

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Poster

PSTR345: Visual Motion Perception

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Program #/Poster #: PSTR345.05/G20

Topic: D.06. Vision

Support: Marie Skłodowska-Curie grant agreement N° 956669

Title: Neuronal processing of long-range apparent motion and related perceptual biases in primates

Authors: *S. GIANCANI[1], M. SRIVASTAVA[2], K. BLAIZE[3], S. CHEMLA[3], A. DESTEXHE[4], M. SZINTE[3], M. DI VOLO[5], A. MONTAGNINI[3], F. Y. CHAVANE[3];
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Marseille Univ., Marseille, France; [4]NeuroPSI, CNRS, Saclay, France; [5]Biosci., CNRS, FRE 3693., Bron, France

Abstract: Neighboring points in the visual field are represented by neighboring neurons in V1, forming a retinotopic map. Using a localized static stimulus, such as a gaussian flash (i.e. stroke) previous results showed that the cortical response corresponds to a traveling wave in V1 (Muller 2014, 2018). A wave in a retinotopic map can be interpreted as a movement in the visual field: in other words, a local static stimulus induce a dynamic cortical response in space and time. But what is the effect when a sequence of static stimuli are presented along a trajectory? Chemla et al (2019) showed that a 2-stroke apparent motion stimulus (AM) induced a coherent cortical motion signal shaped by a systematic suppressive wave propagating in opposite direction to the motion. In this study, we employed a sequence of 3-strokes AM and we measured the response of the V1 neural population in behaving macaques using voltage-sensitive dye imaging (VSDI). Our results demonstrate that, during the 3-stroke sequence the spatial profile of the response to the third dot is significantly modified compared to the single-stroke control. This modification involves the facilitatory activation of the cortex ahead of motion direction and suppression leading to the displacement of the peak of activity in the opposite direction. To further explore this paradoxical phenomenon, we complemented our observation with (i) computational modeling approach, to investigate whether intra-cortical propagation of excitatory and inhibitory activity can explain this dual effect, with (ii) human psychophysics using perceptual or saccade reports, to test how such stimulus affect the perceived position of the last stroke of the same apparent motion stimulus. The model reproduces exactly the dual outcome shown by the neural data, demonstrating that the interplay with inhibition is key to reproduce the results, similar to the inhibition-stabilized mechanism showed in previous studies (Zerlaut 2018, Chemla 2019). The human experiments on the other side, revealed surprising outcomes. Saccade landing task is in line with the mislocation of the peak, lagging behind the expected position, while the perceived position reports are in line with the facilitation in the motion direction, presenting a bias in direction of the motion. Further control experiments showed that as the uncertainty about the perceived position increases, so does the motion-extrapolation bias. These results suggest that the same V1 dynamic, as revealed with VSDI, can lead to two different behavioral outcomes, maybe through different read-out mechanisms by downstream areas.

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Poster

PSTR345: Visual Motion Perception

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.06/G21

Topic: D.06. Vision

Title: A feedforward mechanism for pattern motion encoding in primary visual cortex

Authors: *S. M. GANNON[1], L. JENNINGS[2], J. J. PATTADKAL[2], N. J. PRIEBE[2], L. L. GLICKFELD[1];
[1]Neurobio., Duke Univ., Durham, NC; [2]Neurosci., The Univ. of Texas at Austin, Austin, TX

Abstract: Primates and rodents perceive the pattern direction of motion of drifting plaids despite the divergent directions of motion of the component gratings. Classic models argue that pattern motion perception arises from a two-stage computation where component direction is represented in primary visual cortex (V1) and integrated in higher visual areas by pattern motion selective neurons. However, accumulating evidence of pattern selective neurons in V1 of both primates and rodents has called this model into question. We propose that the pattern selectivity observed in V1 is instead generated by a combination of suppressive and facilitating cross-orientation interactions due to non-linearities in the feedforward visual pathway. We have previously demonstrated that cross-orientation interactions depend on the relative phase of the component gratings, are unaffected by cortical adaptation, and can be predicted by the linear sum of subthreshold inputs. We predict that the same will be true for pattern selectivity in V1. To determine whether pattern selectivity in V1 is phase-dependent, we measured neural responses in both mouse and marmosets to gratings and plaids in which we varied the starting phase of one of the component gratings in increments of 90 degrees. We then calculated a pattern index (Zp-Zc) at each of the four phases. We find that the pattern selectivity of neurons in V1 of both species are significantly modulated by phase compared to controls. Notably, we find very few (if any) truly pattern cells that are phase-invariant in V1 of either species; there is instead a strong positive correlation between the degree of phase modulation and peak pattern selectivity. In support of a role for feedforward processing, we find that L4 neurons in mouse V1 are more strongly modulated by phase than neurons in L2/3. To parse the feedforward contribution to the generation of pattern motion encoding, we measured pattern selectivity after adaptation to one of the component gratings in mouse V1. We find that pattern selectivity is not altered, arguing against a role for the cortical integration of component signals in generation of pattern motion coding. As a next step, we are collecting whole-cell electrophysiology from mouse V1 to determine if phase-dependent pattern motion encoding can be predicted from the linear sum of the subthreshold responses to component gratings presented alone. Overall, our data provides an alternate mechanism for how pattern motion perception arises in primates and rodents.

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Poster

PSTR345: Visual Motion Perception

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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IoE-IISc grant to SPA
Prime Minister's Research Fellowship to SS

Title: Encoding of object bounce trajectories in monkey inferior temporal cortex

Authors: *S. SAHA, S. P. ARUN;
Ctr. for Neurosci., Indian Inst. of Sci., Bangalore, India

Abstract: We need to track and predict trajectories of moving objects to successfully interact with the dynamic world. It is unknown how the visual system combines such information to predict future trajectory of an object given its current state of motion and apparent interaction with another object. To investigate this issue, we created movie stimuli where we independently varied the incidence and bounce angle of a ball that bounced off a static platform. This design gave us two types of movies where bounce either was a physically plausible continuation of the incidence (congruent movies) or it was not (incongruent movies). We then recorded neural responses to these movies from inferior temporal cortex (IT) in monkeys during a fixation task. Our main results are as follows: (1) IT neurons were selective to specific incidence and bounce angles; (2) Neural responses were accurately predicted as a linear combination of incidence and bounce selectivity; (3) IT neurons showed main and interaction effects between incidence and bounce angle during the collision period with platform; (4) IT neurons with significant interaction effects showed higher correlation between incidence and bounce weights, as well as higher model error for congruent compared to incongruent movies; (5) Decoders trained on neural responses to the incidence angle were able to decode the physically plausible bounce angles. Taken together, our results reveal that objects as well as their dynamic physical interactions such as bounces are encoded by higher order visual cortex. We propose that such neural responses form the basis for intuitive physical inference.

Disclosures: S. Saha: None. **S.P. Arun:** None.

Poster

PSTR345: Visual Motion Perception

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Topic: D.06. Vision

Support: CRC-2021-00326
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York University, Provost Fellowship

Title: Probing the interaction of the motion and form of visual objects in macaque inferior temporal cortex

Authors: *J. UWISENGEYIMANA[1], K. KAR[2];
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Abstract: Traditionally, object motion and form have been associated with the dorsal and ventral visual pathways respectively. However, recent studies have challenged this dichotomy. Hong et al. (2016) showed that the ventral stream represents position-related information, and Ramezanpour et al. (2024) demonstrated that object motion can be decoded from the inferior temporal (IT) cortex in the ventral pathway. These findings necessitate a deeper investigation into how the ventral pathway might support both motion and form processing. The interaction between motion and form in the ventral pathway has important implications for understanding visual perception in complex, naturalistic environments. Camouflage is a common strategy employed by many species to avoid detection by predators or prey. We hypothesize that camouflaged scenes represent situations where object motion could facilitate the detection of form-based attributes that are otherwise less observable in stationary scenes. To test this, we adapted 132 videos from the Moving Camouflaged Animals (MoCA) dataset and performed large-scale neural recordings across the IT cortex in two rhesus macaques. We presented 500 ms videos to the monkeys (central 8 deg), while they fixated at the center of the screen. These videos included objects moving in camouflaged backgrounds (from MoCA) or random stationary frames from these videos, each shown for 500 ms.
Consistent with Ramezanpour et al. (2024), we first observed that IT population (86 sites) decodes can significantly predict the velocity of moving objects (Pearson R = 0.25, p=0.004). Interestingly, preliminary results also show that linear decoding of form-related attributes, such as object size, is more correlated with ground truth when using neural responses to the moving stimuli (Pearson R = 0.50) compared to a random stationary frame (Pearson R = 0.4) from these stimuli. This suggests that motion enhances the representation of form-based attributes in the IT cortex.
Our findings provide novel insights into the neural substrates and mechanisms that might support behaviors that rely on the interaction of motion and form. Furthermore, these results provide valuable guidance and constraints for the development of next-generation, dynamic models of visual processing that need to incorporate both form and motion processing. Our results suggest that object motion may play a crucial role in breaking camouflage and enabling the recognition of object form. This has potential applications in fields such as computer vision, robotics, and surveillance, where detecting and recognizing objects in cluttered or camouflaged environments is a significant challenge.

Disclosures: J. Uwisengeyimana: None. **K. Kar:** None.

Poster

PSTR345: Visual Motion Perception

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Topic: D.06. Vision

Support: NIH Grant EY022443

Title: Neural representations of locally paired- and unpaired-dot stimuli moving in different directions in cortical area MT correlate with the perception of integrated motion and motion transparency

Authors: B. GHIMIRE, S. WIESNER, *X. HUANG;
Dept. of Neurosci., Univ. of Wisconsin - Madison, Madison, WI

Abstract: When viewing overlapping random-dot stimuli moving in two directions, human observers usually perceive motion transparency. Psychophysical studies have shown that when dots moving in two directions are locally paired, human subjects perceive the vector-averaged (VA) direction of the two stimulus components, whereas when dots are unpaired, perceive two component directions. The neural basis for this drastic perceptual change is unknown. We recorded from neurons in the middle-temporal (MT) cortex of two male macaque monkeys while they performed a fixation task. Visual stimuli were dots moving at 5º/s in two directions separated by 90º. We varied the VA direction to characterize the direction-tuning curves. In the paired-dot condition, dots moving in different directions were locally paired, with a path length of 0.4º and lifetime of 80 ms. In the unpaired-dot control condition, unpaired dots moved in two directions and had the same path length and lifetime as the paired-dot stimuli. In response to the unpaired dots, MT direction-tuning curves had a bimodal shape. The peak was reached when one of the component directions was aligned with the neuron's preferred direction (PD), suggesting that MT responses represent the component directions. In contrast, in response to the paired dots, the direction-tuning curves of the same MT neurons showed a unimodal shape, and the peak was reached when the VA direction was aligned with the neuron's PD. The direction tuning to the paired-dot stimuli matched well with the tuning curve to a stimulus moving in a single direction, suggesting that MT responses represent the VA direction of the paired-dot stimuli. Timecourse analysis revealed that the direction tuning to the paired-dot stimuli had a unimodal shape at the beginning and was stable throughout the motion period, suggesting that integration of the two component directions may have already occurred in the feedforward signals to MT. Whereas the tuning to the unpaired-dot stimuli initially showed a unimodal shape and, over a period of 70-90 ms, the tuning started to show two response peaks. These results demonstrate a neural correlate in MT of an intriguing perceptual phenomenon that motion transparency can be changed to integrated motion by locally pairing dots. Since local pairing is at the spatial scale of the receptive field size of V1 neurons, it is likely that V1 also plays an important role in the perception of integrated motion and motion transparency. Supporting this idea, our preliminary results showed that direction-selective V1 neurons can differentiate paired-dot from unpaired-dot control stimuli and represent stimulus motion consistent with visual perception.

Disclosures: B. Ghimire: None. **S. Wiesner:** None. **X. Huang:** None.

Poster

PSTR345: Visual Motion Perception

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Program #/Poster #: PSTR345.10/G25

Topic: D.06. Vision

Support: Indiana Traumatic Spinal Cord and Brain Injury Research (ISCBIR) Fund

Title: A mouse model of perceptual decision-making with global motion stimuli

Authors: *E. M. FRAZIER[1], A. B. SERENO[2,1,3], M. C. DADARLAT[1];
[1]Biomed. Engin., [2]Psychological Sci., Purdue Univ., West Lafayette, IN; [3]Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: The perception of visual motion is fundamental for navigating and interacting with our surroundings. Disruptions in the processing of optic flow are characteristic of many neurological conditions and are commonly reported following traumatic brain injury. Despite the utility of mouse models in studying maladaptive changes in the perception of visual motion, few relevant behavioral paradigms are also compatible with *in vivo* neural recordings. Therefore, we developed a novel head-fixed discrimination task to probe perceptual decision-making using a complex visual motion stimulus. In this task, head-fixed mice learn to discriminate the global motion direction (right or left) of a random dot kinematogram (RDK). We varied the reliability of the RDK by decreasing the fraction of coherently moving dots. Mice earned a reward by rotating a wheel beneath their paws to counter the perceived global motion direction and zero the dot field velocity. Motivated mice reliably performed hundreds of trials per training session (45-90 minutes). After training, a pilot group of mice (n = 3, 2M) consistently achieved above 80% accuracy for high coherence stimuli and performed significantly above chance for coherences as low as 20% (56% ± 6%; $p < .001$). Accuracy significantly decreased with decreasing coherence ($p < .001$; repeated-measures ANOVA, RMANOVA). Concurrently, there was a significant increase in response time ($p < .001$; RMANOVA) and an increase in the number of trials in which the mice failed to report a decision within the 30-second response window ($p < .001$; RMANOVA). These findings suggest that mice integrate motion information over time to make accurate sensory decisions, such that they need more time for more ambiguous, low-coherence stimuli. Further, our results demonstrate the robustness of this behavioral paradigm in probing decision-making regarding visual motion perception. Thus, we establish a basis for implementing this task in our future investigations into the hierarchical processing of complex visual motion perception in healthy and dysfunctional states.

Disclosures: E.M. Frazier: None. **A.B. Sereno:** None. **M.C. Dadarlat:** None.

Poster

PSTR345: Visual Motion Perception

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Program #/Poster #: PSTR345.11/

Topic: D.06. Vision

Title: Mapping Neural Responses to Agentive and Physical Movement within Cortical Networks

Authors: *S. AKBIYIK;
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Abstract: Understanding dynamic information is vital for navigating our social and physical environments. Research underscores the role of frontoparietal and posterior temporal cortices in this process, engaged in action planning, recognition, and physical inference. Recent work suggests that while a set of frontoparietal regions function within a domain-general framework for processing physics and kinematics of dynamic scenes, the processing of socially relevant information—e.g. intentions, social interactions, animate motion— involves a right-lateralized set of regions including the superior temporal sulcus, temporoparietal junction, and ventral inferior frontal gyrus. Do the frontoparietal regions involved in processing kinematics of dynamic scenes constitute a domain-general network of interconnected regions, or do they represent a collection of independent systems? Within these frontoparietal regions, are there components that are specifically dedicated to handling socially relevant information, such as the movements of intentional agents? How do frontoparietal regions involved in dynamic scene processing interface with occipitotemporal cortices that are involved in object recognition where distinctions between different domains (e.g. faces, bodies, objects) are emphasized? The current study addresses these questions through examining neural responses to agentive and physical movement within the context of intrinsic functional connectivity. Using precision neuroscience methods, we analyzed response profiles across different task paradigms allowing for direct comparison of recruitment of closely situated brain regions in individual subjects. Participants underwent two 2-hour fMRI sessions including a motion prediction task based on agentive or physical movement, resting state fixation runs, and a category localizer. Through individual subject analyses, we find that event though frontoparietal regions that are involved in dynamic movement processing are largely overlapping for agentive or physical motion, side-by-side regions can show increased recruitment for either domain. Seed- and parcellation-based analyses of resting state functional connectivity reveal that regions with distinct preference profiles belong to separate resting state networks, and those highly recruited for physical movement are interconnected with lateral occipitotemporal object-selective areas. Overall, our findings shed light into the role of various brain regions in processing dynamic scene information as it applies to physical entities and intentional agents.

Disclosures: S. Akbiyik: None.

Poster

PSTR345: Visual Motion Perception

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR345.12/G26

Topic: D.06. Vision

Title: Cooperative thalamocortical circuit mechanism for sensory prediction errors

Authors: *S. FURUTACHI[1], T. D. MRSIC-FLOGEL[2], S. B. HOFER[1];
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Abstract: The brain functions as a prediction machine, utilizing an internal model of the world to anticipate sensations and the outcomes of our actions. Discrepancies between expected and actual events, referred to as prediction errors, are leveraged to update the internal model and guide our attention towards unexpected events. Despite the importance of prediction error signals for various neural computations across multiple brain regions, surprisingly little is known about the neural circuit mechanisms responsible for their implementation. Here we describe a thalamocortical disinhibitory circuit required for generating sensory prediction errors in mouse primary visual cortex (V1). Using calcium imaging with optogenetic manipulations as mice traverse a familiar virtual environment, we show that violation of animals' predictions by an unexpected visual stimulus preferentially boosts responses of layer 2/3 V1 neurons most selective for that stimulus. Prediction errors specifically amplify the unexpected visual input, rather than representing a non-specific surprise or difference signal about how the visual input deviates from animals' predictions. Selective amplification of unexpected visual input is implemented by a cooperative mechanism requiring thalamic input from the pulvinar, and cortical vasoactive-intestinal peptide-expressing (VIP) inhibitory interneurons. In response to prediction errors, VIP neurons inhibit a specific subpopulation of somatostatin-expressing (SOM) inhibitory interneurons that gate excitatory pulvinar input to V1, resulting in specific pulvinar-driven response-amplification of the most stimulus-selective neurons in V1. Therefore, the brain prioritizes unpredicted sensory information by selectively increasing the salience of unpredicted sensory features through the synergistic interaction of thalamic input and neocortical disinhibitory circuits.

Disclosures: S. Furutachi: None. **T.D. Mrsic-Flogel:** None. **S.B. Hofer:** None.

Poster

PSTR345: Visual Motion Perception

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Topic: D.06. Vision

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NIH grant R01EY016454-17
NIH grant U19NS118284-02

Title: A Head-Mounted Lensless Microscope for Mesoscopic Calcium Imaging in Head-unrestrained Non-Human Primates

Authors: *J. WU[1], Y. Y. CHEN[2], A. VEERARAGHAVAN[1], E. SEIDEMANN[2], J. T. ROBINSON[1];
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Abstract: Mesoscopic calcium imaging offers a powerful tool for studying cell-type specific neural activity over large sections of the cortex and over multiple cortical areas. Ideally, one could observe this activity in freely behaving animals, however, existing systems for imaging calcium dynamics over large areas of the brain in non-human primates (NHPs) are large table-top devices that require researchers to restrain the animal's head so that it remains under the lens of the microscope. Here, we present "Bio-FlatScopeNHP", a novel fluorescent imaging device capable of imaging mesoscale calcium activity in non-human primates that are free to move their heads. We successfully miniaturized our system by replacing lenses with an optical phase mask and computational algorithms that reconstruct images from complex sensor data. The resulting lensless microscope can fit comfortably on top of the heads of the NHPs, allowing the animals to move their heads freely while imaging. We demonstrate the capabilities of Bio-FlatScopeNHP by imaging the primary visual cortex (V1) of behaving rhesus macaques, achieving a field of view of approximately 20 mm². We imaged GCaMP signals from V1 on the head-fixed macaque using a tabletop widefield microscope with an sCMOS camera and on the head-unrestrained macaque using Bio-FlatScopeNHP. Large sinusoidal grating at 6 equally spaced orientations (0, 30, 60, 90, 120, 150 degrees) were used as visual stimuli in our experiments. We calculated the orientation columns map from data collected in the same session using the tabletop system during head-fixation and using the Bio-FlatScopeNHP with head-unrestrained. The orientation maps obtained from Bio-FlatScopeNHP and the widefield microscope show significant similarities with a correlation coefficient of 0.72. These results demonstrated that Bio-FlatScopeNHP is capable of capturing calcium dynamics at the columnar scale and, for the first time, capture high quality orientation map information in a head-unrestrained NHP. Our research introduces a novel method for functional mesoscopic imaging using a head-mounted lensless microscope, offering a powerful approach to studying neural activity in freely behaving NHPs. These experiments have the potential to uncover the intricate relationship between neural activity and behavior in more naturalistic settings.

Disclosures: J. Wu: None. **Y.Y. Chen:** None. **A. Veeraraghavan:** None. **E. Seidemann:** None. **J.T. Robinson:** None.

Poster

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Title: Neural feature dimension maps index continuous levels of stimulus salience

Authors: *E. M. MACHNIAK, D. D. THAYER, T. C. SPRAGUE;
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Abstract: Cognitive models of attention state that there are a series of spatial maps that index locations containing important image-salient and goal-relevant items. One such map, the 'priority map', is used to guide what is ultimately selected by attention, with items given a high level of importance selected by visual attention for further processing. This feature agnostic map is computed based on several individual spatial maps that are specialized to compute the importance of items based on individual feature dimensions, such as color or motion (Itti & Koch, 2001). Recently, neural correlates of these 'feature dimension maps' have been identified, with hV4/VO1/VO2 representing a color map, and TO1/TO2 representing a motion map (Thayer & Sprague, 2023). These ROIs are spatially selective and track the location of stimuli that are salient due to high levels of local feature contrast. However, priority map theory predicts that feature dimension maps track the magnitude of stimulus salience. This is necessary to ensure that the most important stimuli are attended, as high feature contrast should be represented more strongly than low feature contrast (Nothdurft, 1993). We tested whether neural color and motion maps represent varying degrees of feature contrast by presenting stimuli comprised of either static colorful dots or black-and-white moving dots. A portion of either dot array was made salient on most trials: colorful arrays could contain dots that were a different color from the rest of the array and some dots in the motion arrays could move in a different direction. Critically, we varied the degree of local feature contrast to determine if responses in neural feature dimension maps tracked the graded levels of salience in the display. We also included a control condition with checkerboard stimuli presented at varying contrasts to ensure that these regions could detect general changes of salience. We used an inverted encoding model to reconstruct spatial maps from these ROIs, which allowed us to assess if the strength of the stimulus representation varied based on the salience of the physical stimulus. When shown the checkerboard stimulus, responses in feature-selective ROIs gradually increased with increasing luminance contrast, meaning that they are sensitive to changes in salience. Additionally, across most levels of feature salience, color- and motion-selective regions had a stronger response when the stimulus was salient based on the ROI's preferred feature, indicating that they are sensitive to even low levels of feature salience. Our results further support color- and motion-selective regions as neural feature dimension maps.

Disclosures: E.M. Machniak: A. Employment/Salary (full or part-time):; University of California, Santa Barbara. **D.D. Thayer:** None. **T.C. Sprague:** None.

Poster

PSTR345: Visual Motion Perception

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Program #/Poster #: PSTR345.15/G29

Topic: I.08. Methods to Modulate Neural Activity

Support: ZIAMH002909

Title: The facilitatory effects of transcranial random noise stimulation on motion processing

Authors: *R. RUHDE[1], M. CARROLL[2], G. EDWARDS[3], C. I. BAKER[4];
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Abstract: Non-invasive brain stimulation (NIBS) techniques have the potential to demonstrate the causal impact of targeted brain regions on specific behaviors, and to regulate or facilitate behavior in clinical applications. Transcranial random noise stimulation (tRNS) is one form of transcranial electric stimulation (tES) where an alternating current is passed between electrodes at random frequencies. High-frequency tRNS (hf-tRNS) is thought to enhance excitability and has been reported to have facilitatory effects on behavior in healthy and clinical populations. Due to the potential application of hf-tRNS, clear demonstrations of the efficacy and replicability of stimulation are critical. Here, we seek to replicate the facilitatory effect of hf-tRNS over the human middle temporal complex (hMT+) on contralateral motion processing, initially demonstrated by Ghin et al. (2018). The reported improvement in performance was specific to global motion processing in the visual field contralateral to stimulation. The motivation to replicate this specific effect was reinforced by the well-supported hypothesis that hMT+ is critical for contralateral global motion processing. We used a within-participants design in which each participant (n=42) completes a global motion discrimination task during three stimulation conditions: active hf-tRNS targeting hMT+, sham hf-tRNS targeting hMT+, and an active control hf-tRNS applied to the forehead. Following Ghin et al. (2018), hMT+ was localized using anatomical landmarks (3 cm dorsal of inion and 5 cm leftward). We analyze the motion coherence threshold in the contralateral visual field relative to the ipsilateral visual field to test for a decrease in the contralateral field threshold in response to stimulation. We are also investigating the effect of stimulation targeting hMT+ relative to sham and active forehead control conditions. Finally, we included a functional MRI localizer of hMT+ to explore the overlap between the simulated e-field of the anatomically and functionally localized hMT+ to determine if an increased overlap predicts increased behavioral response to stimulation.

Disclosures: R. Ruhde: None. **M. Carroll:** None. **G. Edwards:** None. **C.I. Baker:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

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Program #/Poster #: PSTR346.01/G30

Topic: D.06. Vision

Support: NIH Grant R15NS121788

Title: Inferences on face fusiform area function: comparing responses to identical and different visual categories and face stimuli

Authors: *K. ORGO[1], N. BRUNET[2];
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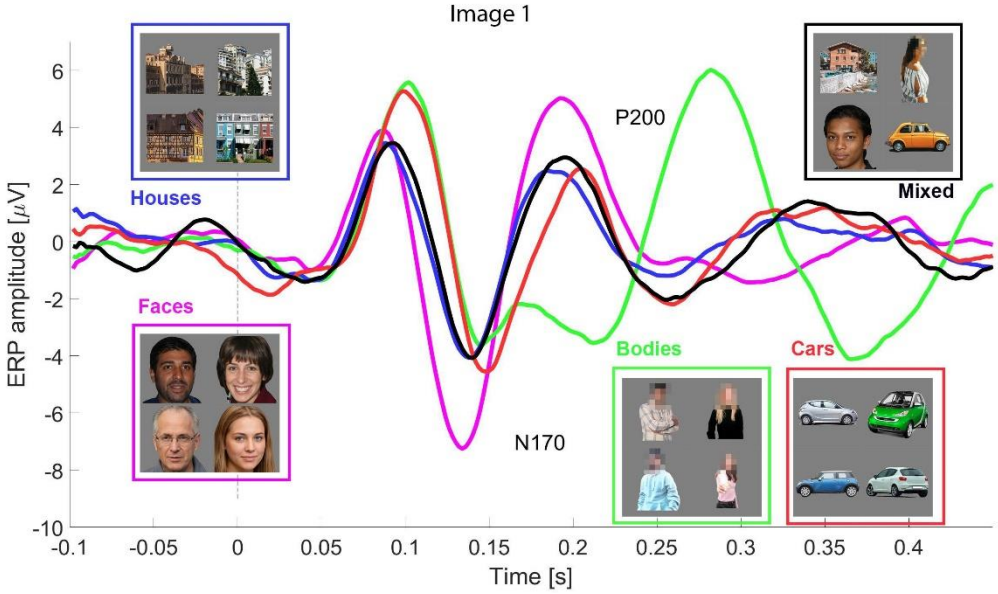
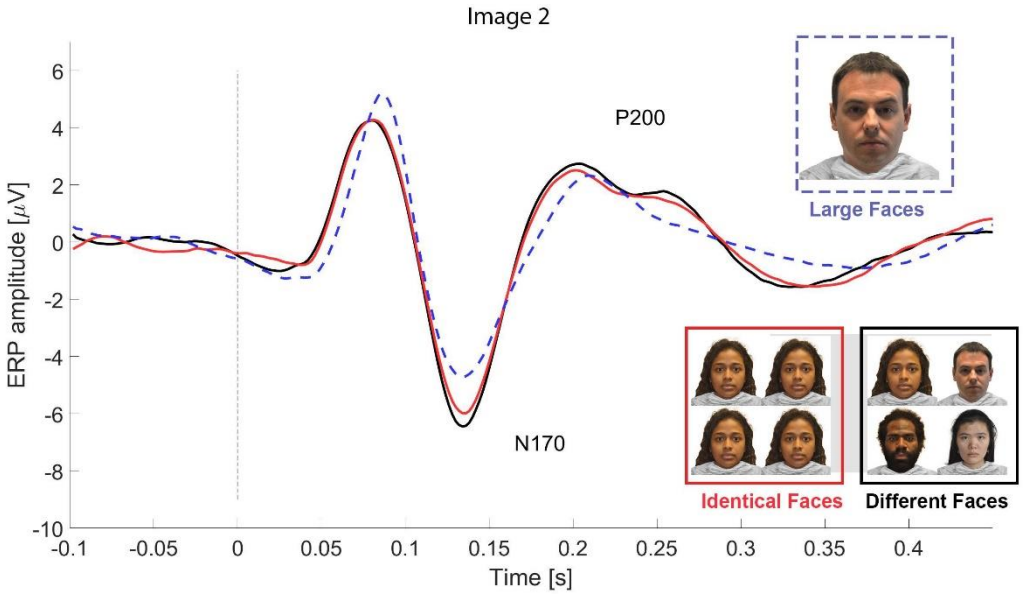
Abstract: In this study, we investigate the effect of displaying four different images simultaneously on event-related potential (ERP) waveforms, focusing particularly on the N170 component associated with face processing in the fusiform face area (FFA). Participants were presented with different combinations of images during two experiments. In the first experiment (Image 1), each trial displayed four images, either belonging to the same visual category (faces, bodies, buildings, or cars) or across different categories. Careful attention was given to ensure a balanced placement of the four images within the visual field across different trials. Results from Experiment 1 revealed very distinct ERP waveforms in response to the different visual stimulus categories, with faces eliciting a prominent N170 response compared to other categories. Interestingly, while N170 responses were observed across all stimulus categories, the mixed-category conditions produced weaker N170 responses. Experiment 2, demonstrated that viewing four different faces evoked a larger N170 compared to viewing four identical faces or one large face (Image 2). These findings suggest that the FFA contains a population of neurons sensitive, but not exclusively selective, to faces, rather than neurons exclusively responding to non-face stimuli. Additionally, the enhanced N170 response to diverse faces implies its capacity to distinguish between different faces, providing temporal insights into the role of the FFA in face recognition.





Disclosures: K. Orgo: None. **N. Brunet:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

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Program #/Poster #: PSTR346.02/G31

Topic: D.06. Vision

Support: STI2030-Major Projects (2022ZD0204600)

Title: Neural representation of texture-perturbed face images in the macaque anterior medial face patch

Authors: *W. DAI, L. CHANG;
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Abstract: We can robustly recognize the identity from a face image under various unnatural conditions, including texture stylization and image distortion. One potential area crucial to robust face recognition is the anterior medial face area (AM) as the neural representation of facial identity in AM achieves invariance to a wide range of views, scales, and positions. However, it remains unclear whether the identity representation in AM is robust to more complex transformations such as stylization, and how the transformation affects the identity representation in AM. One possibility is that AM neurons are sensitive to stylization, since the majority of AM neurons are more strongly tuned to ‘texture’ features of an active appearance model than to shape features (Chang & Tsao, 2017). Another possibility is that AM neurons are resistant to

these changes, consistent with our perception. Here, we addressed this issue by designing a stimulus set containing natural human faces, natural monkey faces, and unnatural faces generated by perturbing these natural faces in diverse ways. Perturbations included texture stylization and low-level feature distortion in three magnitudes. For each magnitude, we found that both category and identity information were preserved at the population level. The majority of AM neurons maintained the identity preference for texture-stylized faces similar to natural faces, albeit the similarity decreased with respect to perturbation magnitude. Interestingly, a subgroup of AM neurons showed a high correlation ($r>0.8$) between the texture preference for stylized faces and the preference for texture-only images, where no facial information was present. Our preliminary results suggest that AM neurons robustly encode facial identity despite drastic texture stylization and respond selectively to different texture styles at the same time.

Disclosures: W. Dai: None. **L. Chang:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

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Program #/Poster #: PSTR346.03/G32

Topic: D.06. Vision

Support: ERC 2019-SyG-RELEVANCE-856495

Title: Voxelwise encoding of biomechanics in occipitotemporal cortex using dynamic body stimuli at ultra-high field 7T

Authors: *G. MARRAZZO[1], F. DE MARTINO[1], A. MUKOVSKIY[2], M. A. GIESE[2], B. DE GELDER[1];
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Abstract: In this fMRI study we investigated the role played by biomechanical plausibility in the representation of bodies in EBA. The extrastriate body area (EBA) (Downing et al. 2001, Peelen and Downing, 2005) is currently considered to be a ventral cortex object category area, selective for body stimuli but little yet is understood about its computational functions. In a previous study we showed that the EBA is sensitive to joints position in still body stimuli (Marrazzo et al. 2023). Here, we used video images to investigate whether disrupting joints configuration affects the representation of bodies in EBA. Stimuli depicted artificial whole-body movements and were generated from the MoVI dataset. We selected 60 trials of naturalistic body movement and created 60 (possible) videos. Additionally, these stimuli underwent further processing where elbows and knees position/angle were manually modified, to create (from possible stimuli) biomechanically impossible stimuli. Therefore, the stimuli set included 120 videos (60 possible, 60 impossible). 12 participants were scanned using a 7T (T2*-weighted Multi-Band accelerated EPI 2D BOLD sequence, MB = 2, voxel size = 0.8 mm^3, TR = 2300 ms, TE = 27 ms) in a fast

event-related design over 12 separate runs. Each run consisted of 20 unique stimuli (10 possible, 10 impossible repeated 6 times across the 12 runs) which appeared on the screen for 2-3 s. Participants were asked to fixate and attention was controlled using catch trials (fixation shape change). The fMRI response was modeled using several features extracted from the stimuli: 3D coordinates and rotation matrices of key joints (kp/rot) and a model which represents within\between distance between joints for each video as a mean to encode biomechanical information (simdist). The fMRI predicted responses from each model were generated via banded ridge regression (Nunez-Elizalde et al. 2019, Dupré La Tour et al. 2022) using crossvalidation. Results show a pattern of responses across visual cortex with simdist and kp model best predicting responses to our stimuli. Specifically, the simdist representation shows higher prediction accuracy in in high-level temporal areas such as EBA outperforming the kp model. These findings expand on previous research showing that EBA codes for specific features of the body, which in the case of kp model, are the joints position (Marrazzo et al. 2023). Additionally, EBA shows high degree of sensitivity for joints configuration to the point that biomechanically possible/impossible bodies appear to be differentially encoded.
Acknowledgments: This work was supported by ERC 2019-SyG-RELEVANCE-856495

Disclosures: G. Marrazzo: None. **F. De Martino:** None. **A. Mukovskiy:** None. **M.A. Giese:** None. **B. de Gelder:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

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Topic: D.06. Vision

Support: ERC 2019-SyG-RELEVANCE-856495

Title: Perception of conspecific facial expressions by macaque monkeys in a behavioral paradigm transcends expression morphology

Authors: *R. SIEBERT[1,2], N. TAUBERT[3], M. A. GIESE[3], P. THIER[1];
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Abstract: The ability to interpret facial expressions of conspecifics is an important social skill for primates. Macaque monkeys communicate using relatively stereotyped facial configurations. However, whether these configurations are also perceived in a comparatively stereotyped manner is little explored, but nonetheless has been widely assumed.
In order to formally test this hypothesis, we trained male rhesus macaques in a forced-choice task to categorize four facial expression types (fear grin, lip smack, threat and neutral) by associating

each expression category with a differently colored target located in one of the four corners of a computer screen. They first watched a 1-2 s video of a conspecific making a particular facial expression, were then presented with the four targets and then had to make a saccade to the correct target. Once the monkeys had mastered this task on the basis of a diverse training set (13 videos per expression category), we showed new videos in catch-trials, presented interleaved with trials from the training set. In the catch-trials the monkeys were rewarded for choosing any one of the targets. The catch-trial video set comprised filmed real monkeys, new monkey identities and previously seen monkeys with previously unseen expression categories, as well as a naturalistic monkey avatar displaying the four facial expressions.
The monkeys partially generalized to the catch-trial (i.e. the untrained) expression videos produced by the real monkeys and the avatar. However, only the threat expression was reliably categorized as such. Often, a dichotomy emerged, in which lip smacking and neutral were categorized similarly and distinctly from threat, whereas the fear grin tended to be lumped together with either lip smack or threat. The monkeys seemed to interpret these configurations flexibly beyond the stereotyped morphology, presumably based on the potential behavioral consequences of these expressions. They are likely to use facial cues that reflect the arousal and valence features of the signaler´s context as well as information on the personality characteristics of the signaling monkey.
As the monkeys' behavior did not confirm preconceived human categorizations of macaque facial expressions, our results caution against the thoughtless use of such stimuli in scientific studies.

Disclosures: R. Siebert: None. **N. Taubert:** None. **M.A. Giese:** None. **P. Thier:** None.

Poster

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Support: ERC 2019-SyG-RELEVANCE-856495
HFSP RGP0036/2016
BMBF FKZ 01GQ1704

Title: Encoding of bodies and objects in body-selective neurons

Authors: *A. LAPPE[1,2,3], A. BOGNÁR[4], G. GHAMKHARI NEJAD[4], A. MUKOVSKIY[5], M. A. GIESE[5], R. VOGELS[4];
[1]Univ. of Tübingen, Tübingen, Germany; [2]Hertie Institute, University Clinic Tübingen, Tübingen, Germany; [3]International Max Planck Research School for Intelligent Systems, Tübingen, Germany; [4]KU Leuven, Leuven, Belgium; [5]Hertie Inst., Univ. Clin. Tübingen, Tübingen, Germany

Abstract: The primate visual system has evolved subareas in which neurons appear to respond more strongly to images of a specific semantic category, like faces or bodies. The computational processes underlying these regions remain unclear, and there is debate on whether this effect is in fact driven by semantics or rather by visual features that occur more often among images from the specific category. Recent works tackling the question of whether the same visual features drive responses of face-selective cells to face images and non-face images have yielded mixed results. Here, we report findings on shared encoding of body and object images in body-selective neurons in macaque superior temporal sulcus. We targeted two fMRI-defined regions, anterior and posterior body patches in two awake macaques using V probes, recording multi-unit activity in and around these patches. In a first phase, we recorded responses to a set of 475 images of a macaque avatar in various poses. We then trained a deep-neural-network based model to predict responses to these images, and subsequently evaluated the model on two sets of object and body stimuli consisting of 6857 and 2068 images, respectively. These images comprised a variety of object types and animal species. After the inference process, we selected the highest and lowest predicted activator for each recording channel from both object and body images. In a second phase, we recorded responses of the same multi-units to these stimuli. For analysis, we only kept those multi-unit sites with high test/retest reliability. Also, we only considered multi-unit sites for which the selected bodies elicited a significantly higher response than the selected objects. We then tested whether the high-predicted objects/bodies indeed lead to higher responses at the corresponding electrode than the low-predicted ones. Across neurons, we found a significant preference of the high-predicted stimulus for both objects and bodies. The highly-activating objects consisted of a variety of everyday objects and did not necessarily globally resemble a body. Furthermore, the correlations between predicted and recorded responses to the objects were consistently positive for both monkeys and recording areas, meaning that the model was able to predict responses to objects after having only been trained on images of a macaque avatar. Our results show that the feature preferences of body-selective neurons are at least partially shared between bodies and objects. On a larger scope, we provide further evidence that category selectivity arises due to highly shared visual features among category instances, rather than semantics.

Disclosures: A. Lappe: None. **A. Bognár:** None. **G. Ghamkhari Nejad:** None. **A. Mukovskiy:** None. **M.A. Giese:** None. **R. Vogels:** None.

Poster

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KU Leuven grant C14/21/111

Title: Keypoint-based modeling of body posture selectivity of macaque inferotemporal neurons.

Authors: *R. VOGELS[1], R. RAMAN[1], G. GHAMKHARI NEJAD[1], A. MUKOVSKIY[2], A. LAPPE[2], M. A. GIESE[2], L. MARTINI[2], A. BOGNÁR[1];
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Abstract: Non-verbal social communication relies on the interpretation of visual cues from the body. fMRI studies in macaques have identified regions within the inferotemporal (IT) cortex that exhibit heightened activation to bodies compared to faces and objects. Among these regions, the ventral bank Superior Temporal Sulcus (STS) patches, i.e. the mid STS (MSB) and anterior STS body patch (ASB), show selectivity for static (and dynamic) bodies. However, the body features that drive the response of these neurons, in particular their representation of body posture, within these two levels of processing are unclear. To investigate this, we recorded multi-unit responses, using 16-channel V-probes, within and around MSB and ASB in two monkeys, employing a stimulus set comprising 720 stimuli featuring a monkey avatar in 45 body postures, rendered from 16 viewing angles. The static stimuli were presented during passive fixation. We employed principal component regression to model the response of the neurons based on the 10 principal components of 22 2D body keypoints extracted from the stimuli, which explained about 90% of the stimulus variance. Of the body-category selective neurons (at least twofold higher response to dynamic bodies compared to dynamic faces and objects), the 2D key-point-based model explained the selectivity for body posture and view with a median reliability-corrected coefficient of determination of 0.42 and 0.20 in the MSB and ASB regions, respectively. Inclusion of the depth dimension increased the model fit significantly for ASB but not MSB. When comparing with a convolutional neural network (CNN; ResNet50-robust; regression on 50 PCs) feature-based approach, the keypoint-based model exhibited slightly inferior performance, particularly in ASB, when focusing on higher-layer features but remained superior to the lower-layer features-based CNN model. Inverting the keypoint models allowed visualization of the body features that drove the posture selectivity of the neurons. We found that these body features ranged from local body features like the upper limbs or tail to combinations of them, but rarely the entire body. Some neurons, even in the mid STS region, tolerated changes in the view of the preferred body parts. The view tolerance was significantly greater in ASB compared to MSB. Our study shows that a body keypoint representation explains a sizable proportion of the selectivity to body posture and view of macaque visual cortical neurons, especially in the mid STS. Furthermore, the modeling suggests that 3D cues contribute to the body selectivity of anterior but not posterior IT neurons.

Disclosures: R. Vogels: None. **R. Raman:** None. **G. Ghamkhari Nejad:** None. **A. Mukovskiy:** None. **A. Lappe:** None. **M.A. Giese:** None. **L. Martini:** None. **A. Bognár:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

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Program #/Poster #: PSTR346.07/G36

Topic: D.06. Vision

Support: ERC Grant 295673
ERC Synergy Grant 856495
FET Proactive Program 824160
FET Industrial Leadership Program 825079

Title: The integration of short- and long-range motion in dynamic body perception revealed by ultra-high field 7T human fMRI

Authors: *B. LI[1], R. VOGELS[2], B. DE GELDER[1];
[1]Univ. Maastricht, Maastricht, Netherlands; [2]KU Leuven, Leuven, Belgium

Abstract: Perceiving the body movements of others is a critical skill for humans and non-human primates. While most studies have focused on perception of body structure and shape, it is unclear how the motion information is integrated into body movement perception. However, in naturalistic images motion and structure are always tightly coupled, making them difficult to disentangle. Therefore, in the current study, we designed a novel set of videos to dissociate the short-range motion of the coherent motion from the long-range structure movements. Each video consists of ten discrete posture phases of particular naturalistic body movements. For each phase, the short-range motion was reconstructed within the posture silhouette by applying the optical flow of the original movements to a salt-and-pepper noise pattern. The silhouette contours were further eliminated by applying non-coherent motion to the background. The short- and long-range motion could then be dissociated by applying either the congruent or incongruent optical flow of the corresponding postural movements. Results of our 7T fMRI study revealed activation changes from long-range shape motion, short-range surface motion and their interaction in both the superior temporal sulcus and occipitotemporal regions. Moreover, we found multiple adjacent clusters in both regions showing modulations for different types of motion, which suggested a fine-grained cortical organization for the integration of long- and short-range motion.

Disclosures: B. Li: None. **R. Vogels:** None. **B. de Gelder:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

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Topic: D.06. Vision

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NIH P30EY012196
Whitehall Foundation 2023-12-117

Title: The histo-architecture of inferotemporal face patches in macaques

Authors: *H. OISHI[1], V. K. BEREZOVSKII[2], M. S. LIVINGSTONE[2], K. S. WEINER[3], M. J. ARCARO[4];
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Abstract: Among primates, face recognition is supported by a network of interconnected cortical regions, known as face patches. While functional magnetic resonance imaging (fMRI) and electrophysiological studies have elucidated functional distinctions between face patches in the inferotemporal (IT) cortex, as well as how they develop, the histo-architectonic features that underlie these functional distinctions remain largely unexplored.This gap in knowledge persists because examining the ground truth, histo-architecture of functionally localized face patches in the same individual requires a unique combination of in-vivo fMRI to localize face patches and post-mortem histological measurements. Here, we solved this problem by developing a novel method to integrate fMRI and histological data from the same individuals. This approach enables us to quantify various histo-architectonic features of face patches (e.g., cytochrome oxidase [CO] and myelin), as well as their layer specificity (e.g., outer and inner layers).These measurements uncovered a complex relationship between functionally defined face patches and underlying histological architecture with three key findings. First, IT face patches differed from one another based on the intensity of their laminar staining, with CO showing more pronounced differences than myelin. Second, CO staining was specifically stronger in the middle lateral face patch (ML), a region thought to be homologous to the human Fusiform Face Area(s) particularly in its outer layers. Third, the differences in CO staining were strongest when face patches were identified based on each animal's fMRI activations rather than using a group probabilistic atlas of face patches (independent of the individual data), underscoring the precision of our methodological approach.These findings demonstrate that this approach bridges the divide between macroscale functional neuroimaging and microscale histological analyses, enabling the quantitative comparisons of histo-architecture across functionally defined regions in the same individuals.

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Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

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Title: Similar Low-Dimensional Encoding Models for Body Category Classification and Identification

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Abstract: The inferotemporal cortex (ITC) is a crucial brain region in primates for object recognition, containing multiple areas showing category-specific responses, such as face patches and body patches. Neurons in these regions not only display a strong preference for specific categories but also distinguish between individual identities within those preferred categories. However, whether these regions employ similar encoding rules to represent between-category and within-category information remains unclear. Although attempts to address this question have been explored within the face patches, revealing that neurons rapidly change their encoding rules, little is known about other category-specific regions (Shi et al., 2023).
To bridge this gap, we recorded the cortical responses in macaque anterior ITC to 1,600 images for animal bodies and general non-animal objects with wide field calcium imaging. For each stimulus category, we built encoding models of cortical activity using principal components (PCs) derived from deep neural network's responses, which were then used to predict responses to the other category. Our findings reveal that models incorporating all PCs, which were built based on within-category stimuli, effectively predict category selectivity. However, they exhibit variability in their image-by-image generalizability to the other category across different cortical sites. Interestingly, reduced encoding models that include only the first five PCs still maintain the ability to predict selectivity and generalization. In contrast, models using the remaining PCs solely explain within-category responses, with no generalization capability, indicating that cross-category generalization primarily stems from the first five PCs. Direct comparisons of representational similarity across categories show that the first five PCs consistently represent both body and non-body objects similarly, whereas later components display diverse tuning patterns. This variability is not due to an out-of-distribution problem or increased tuning noise in later components. These results suggest that the ITC utilizes similar encoding strategies for different categories in a low-dimensional space to detect and identify categories, while employing specialized tuning in a high-dimensional space for more precise identification.

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Poster

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Title: Comparison of face-related activity between superior colliculus and cortical face patches in macaque

Authors: *G. YU[1], K. W. KOYANO[2], L. N. KATZ[3], W. ROBISON[4], D. A. LEOPOLD[5], R. J. KRAUZLIS[1];
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Abstract: Face processing has been extensively studied in higher-order visual cortex (e.g., cortical 'face patches'). Recently, we reported that neurons in the macaque superior colliculus (SC) display a short-latency preference for faces that seems complementary to face processing in cortex: it is coarser but much faster and operates equally well at both peripheral and foveal locations. Here we assessed this complementarity by directly comparing face-related responses in the SC to cortical face patches, using the same image set and paradigm. We recorded neurons in the SC and four face patches (middle fundus, MF; anterior medial, AM; perirhinal, PR; prefrontal orbital, PO), under foveal and peripheral (8° contralateral) presentation conditions. A preference for images of faces over non-faces was observed in all areas. The latency and magnitude of the preference, however, varied across areas and depended on presentation condition. In the foveal condition, a face preference emerged in SC already at 40ms following image onset (median across neurons). In the face patches, face preference latencies were substantially longer (MF, ~80ms; AM, ~110ms; PR, ~120ms; PO, ~140ms). As such, the presence of a face image could be decoded from single SC neurons already at 50ms following image onset with moderate accuracy (area under the receiver operating characteristic curve, AUC, of 0.58). In contrast, decoding based on cortical face patch neurons at that time was at chance. At a later time, 110ms following image onset, faces could be decoded equally well from the SC and most face patches (SC, 0.56; MF, 0.6; AM, 0.53; PR, 0.52; PO, 0.5). In the peripheral condition, face preference latencies remained short in the SC but were significantly delayed in face patches (SC: 41ms; MF, ~140ms; AM, ~120ms; PR, ~130ms; PO, ~160ms). At both 50ms and 110ms following image onset, decoding from the SC was fair (AUC of 0.55 and 0.56 respectively) but at chance for the face patches. Overall, this direct comparison shows that a face preference emerges earlier in SC than in cortical face patches, that the magnitude of this preference in SC is equally strong for both foveal and peripheral presentations, and that in contrast, the magnitude in face patches shows a strong bias towards central vision. Our results support the idea that SC and visual cortex provide complementary functions in the primate visual system for processing faces - rapid face detection in the visual periphery by the SC followed by more detailed foveal analysis by face-selective neurons in visual cortex.

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Poster

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Title: Retcat localizer: stimulus set for simultaneously mapping retinotopic and category-selective brain regions

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Abstract: In order to study the function of visual cortex, researchers define retinotopic and category-selective regions in individual human brains using fMRI. Typically, retinotopic areas (V1, V2, V3, hV4, VO, LO, TO, V3ab, and IPS) are defined using traveling-wave stimuli with bars (Dumoulin and Wandell, 2008), while high-level category-selective regions are defined using functional localizers with images from various categories (Kanwisher et al., 1997; Stigliani et al., 2015). However, conducting two separate experiments is not time efficient, which is especially problematic for populations that are difficult to scan, such as infants, children, and patients. Here we developed a method that generates an optimal stimulus sequence for a RetCat localizer that maps both retinotopic and category-selective regions in a single experiment. We hypothesized that stimuli should contain local contrast varying across the visual field and naturalistic content. Thus, we used a generative neural network, Stable Diffusion (Rombach et al., 2022), trained on large-scale datasets with classifier-free guidance (Nichol et al., 2021) to generate images for the experiment. In each step of the iterative image denoising process, images were conditioned to 1) minimize covariance between 100 fMRI time courses predicted from 100 population receptive fields (pRFs) across locations and sizes that tile a 12° visual field, and align with 2) text prompts that describe six categories: faces, bodies, objects, places, words, and food. We first tested the feasibility of mapping retinotopic regions by testing if we can recover the ground-truth pRF parameters from synthetic time courses with additive fMRI noise generated by the planned stimuli sequences. Results show that we can recover pRF parameters with median absolute percentage errors ~20%. During the experiment, each image was presented 4 times over a 4 seconds trial (on-duration 0.6 s, off-duration 0.4 s), images from different categories were presented in random order and participants (n=4) were instructed to do an RSVP task on fixation. From fMRI, we were able to obtain retinotopic maps (polar angle, eccentricity, pRF size) and category-selectivity maps. Maps were comparable to traveling-wave and functional localizer data in the same participants and we were able to use them to define boundaries of visual regions. These results demonstrate the possibility of using generative neural networks to create optimal and efficient experiments to map different brain regions.

Disclosures: I. Kim: None. **Z. Weng:** None. **K. Grill-Spector:** None.

Poster

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Topic: D.06. Vision

Title: Two functionally distinct areas for face processing in the anterior temporal lobe

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Abstract: Face processing in primates is thought to be supported by a collection of brain areas within the ventral visual stream, with a hierarchical organization along a posterior-to-anterior axis. However, face areas within the human anterior temporal lobe (ATL) remain poorly understood due to signal dropout in fMRI data resulting from magnetic susceptibility artifacts. Our recent work (Deen et al. 2023, "A familiar face and person processing area in the human temporal pole") identified two distinct face areas within the ATL: one in the temporal pole (TP) and one in the perirhinal cortex (PR). Here, we replicate and extend these results using a large dataset of healthy young adults from the Human Connectome Project. We selected a subset of N = 864 participants based on quality control measures provided with the dataset, along with a head motion cutoff (mean framewise displacement of .3mm). TP and PR were anatomically defined using a probabilistic atlas of hand-drawn regions from a separate set of human participants. Face-preferring functional regions-of-interest (ROIs) were defined using a visual category localizer task. We confirmed the presence of face-selective responses within both TP and PR, extending evidence for selectivity to additional control categories (bodies and tools). Next, we assessed the functional connectivity of face-preferring TP and PR using resting-state data. Consistent with our previous results, TP showed stronger functional connectivity with areas within the default mode network (including the medial prefrontal cortex, medial parietal cortex, and temporo-parietal junction). In contrast, PR showed stronger functional connectivity with other face areas within the ventral visual stream. These results provide converging evidence for two functionally distinct face areas within the anterior temporal lobe with dissociable patterns of whole-brain connectivity.

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Title: Neural models for the visual recognition of static body poses and dynamic body movements

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Abstract: For social species, the visual recognition of bodies and body actions is important for survival. The neural circuitry underlying the visual processing of dynamic bodies is not yet well understood. To investigate this processing, we employed two different computational modeling approaches as detailed below.
We previously developed a neurodynamical model of the recognition of dynamic bodies, combining an image-computable model that produces vectors describing the shape of silhouettes with a hierarchical neural field model (recurrent neural network). It successfully reproduces aspects of the population response of neurons in the rostral dorsal bank of the macaque superior temporal sulcus (STS). The higher-level model neurons are sequence-selective and primarily driven by dynamic stimuli. However, recent electrophysiological data from body-responsive regions in the STS and anterior inferotemporal cortex (IT) showed that these neurons exhibit a range of sequence-selectivity, and different levels of tuning to dynamic versus static body stimuli. To model this spectrum of response properties, we simulated multiple neural fields with different parameters, varying the model's lateral interaction kernel. We presented the model with the macaque silhouette video stimuli used in the experiments, consisting of 20 videos, their time-reversed versions, and 200 snapshot images extracted from the videos. We quantified the sequence-selectivity and static/dynamic stimulus tuning of the model neurons and obtained a wide range of values, as in the experiments. The model suggests that simple variations in the recurrent neural dynamics of the neural sub-populations can account for such differences.
An alternative explanation for the observed variation of tuning properties is the varying contributions of the ventral (shape) and the dorsal (motion) visual streams in the recognition of dynamic bodies. To model these pathways, we trained a two-stream deep-learning architecture on a video dataset, UCF5, consisting of 5 human actions. The model consists of two X3D backbones, one (X3D M) for the ventral stream and the other (X3D S) for the dorsal stream, which also relies on explicit optic flow computation. As an initial experiment, we tested the model on videos lacking texture and shape information (from the Appearance Free Dataset), from the same action categories it was trained on. We found that the model shows partial generalization without any training on this dataset, laying the groundwork for enhanced performance with further structural refinements, and comparisons with psychophysical and electrophysiological data.

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Poster

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Title: Representation of faces and objects by cortical neuron populations in marmoset face area PD

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Abstract: A major challenge to uncovering the computations and circuits that enable face perception is the disparity in the scales at which the face-processing system has been studied. We know a great deal about the broad properties of face areas from fMRI and individual 'face cell' tuning properties from single-cell electrophysiology. However, it remains difficult to investigate how populations of face cells work together to represent faces without simultaneous activity measurements from many individual face cells. To fill this gap, we developed an approach for recording calcium dynamics from inferotemporal cortical neuron populations in awake, head-restrained marmosets using two-photon microscopy. Using this approach, we recorded from thousands of neurons within and surrounding the posterior dorsal (PD) face area in marmoset monkeys. We will present analyses of this data that provide insights into how face and objects are represented by neuron populations in PD.

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Poster

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Title: Spatial computations in ventral and lateral visual streams differ across categories and are mature by adolescence

Authors: *J. K. YAO[1], J. CHOO[2], D. FINZI[1], K. GRILL-SPECTOR[1];
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Abstract: Reading and face recognition, skills essential for children's academic performance and socioemotional development, utilize central vision and depend on spatial computations of population receptive fields (pRFs) - parts of visual space processed by groups of neurons in visual cortex. However, it is unknown how pRFs differ across multiple category-selective regions and development. Using a novel pRF mapping fMRI experiment (toonotopy; Finzi et al., 2021) that better drives high-level regions, we assess how spatial computations in ventral and lateral retinotopic and category-selective regions change across development. 17 children (ages 10-17) and 27 adults (ages 22-32) completed toonotopy, featuring sweeping bars (5.7º, FoV: 40º x 40º, 8Hz) with cartoon images, and a visual category localizer (Stigliani et al., 2015). In each subject, we generated from the former, eccentricity, phase, and size maps and from the latter, contrast maps of faces, words, bodies, and places vs. all other categories. Using these maps, retinotopic (V1-VO) and category ROIs in the ventral and lateral streams were manually defined. pRF parameters (location and size) were estimated for each voxel and compared across ROI, hemisphere, and age. We find that toonotopy reliably drives early through high-level visual cortex in children, and adults. In retinotopic visual areas (V1 - VO), linear mixed models reveal little to no development in pRF properties ($Fs < 4$, $p > .04$) but show ROI differences ($Fs > 3$, $p < .02$). In ventral category ROIs, there is no development ($Fs < 1$, $p > 0.5$) but we find a significant interaction between hemisphere and ROI for pRF location and eccentricity ($Fs > 3$, $p < .05$). Ventral place ROIs are more peripheral than face, word, and body ROIs, and face and place ROIs are more peripheral in the left than the right hemisphere. Additionally, body ROIs have a lower visual field bias (VFB), left place ROIs have an upper VFB and right word ROIs have a lower VFB.The lateral stream also shows no development ($Fs < 1.1$, $p > .3$) and different pRF properties across ROIs (main effect of ROI: $Fs > 2.34$, $p < .04$). Across streams, we observe differences in eccentricity whereby pRFs in face and body ROIs are more peripheral in the lateral than ventral stream. Our results reveal that pRF properties are mature by late childhood and vary significantly across hemisphere, category ROIs, and processing streams. Taken together, this might suggest that differences in pRFs across streams may support different visual functions whereas differences in pRFs across categories may mirror differences in viewing behaviors associated with reading, face recognition, and navigation.

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Poster

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Title: Dynamic properties of stimuli drive differential responses in category-selectivity between lateral and ventral cortex

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Abstract: Efficient visual perception is essential for interacting with the world around us and is accomplished through processing across anatomically and functionally distinct visual streams. Both ventral and lateral visual streams contain clustered and distributed responses to visual categories, with the lateral stream thought to be more strongly activated by moving and transient stimuli. However, it is unknown how motion and transients modulate category responses across lateral and ventral streams. Here, we use fMRI to investigate how different aspects of dynamics drive clustered and distributed category representations in the lateral and ventral streams. 10 participants were scanned while viewing stimuli from 8 categories: faces, hands, whole bodies, animals, vehicles, balls, scenes, and pseudowords, and 2 motion conditions: dynamic videos and static images. 4s trials contained a single, full-color exemplar shown on a still gray phase-scrambled background. Exemplars were identical across motion conditions and were either naturally moving or shown on (800ms) and off (200ms) 4 times. We defined anatomical ROIs in each participant in the ventral stream: ventral temporal cortex (VTC), and lateral stream: lateral occipitotemporal cortex (LOTC) and superior temporal sulcus (STS), and analyzed both clustered and distributed responses. We find that both clustered and distributed responses varied across streams. In VTC, we find distinct distributed responses by category that are similar across motion conditions. In contrast, in LOTC and STS, distributed responses within dynamic and transient static motion conditions are more distinct than responses within category conditions. Additionally, we find that LOTC and STS mean responses to animate categories (faces, bodies, and animals) are significantly stronger for moving than static transient stimuli while responses in the VTC for the same categories are similar across motion conditions. Together, these data suggest that differential representations for category and motion information across ventral and lateral regions provide distinct visual functions for the same visual inputs.

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Poster

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Title: Probing the neural code for multiple objects: Identity and numerosity encoding in macaque inferior temporal cortex.

Authors: *J. SHANG[1], H. I. SOMPOLINSKY[2], G. KREIMAN[3], K. KAR[4];
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Abstract: How does the brain process multiple objects? While single-object representations in the macaque ventral stream, specifically in the inferior temporal (IT) cortex, have been extensively studied, the neural mechanisms underlying multi-object perception remain poorly understood. To address this, we recorded neural activity across the IT cortex of rhesus macaques, viewing images containing multiple objects (two or three) within their central visual field. We used 6720 images across 10 object categories (e.g., bear, apple, chair) in varying positions, sizes and rotational poses. We presented each image for 100 ms, followed by a 100 ms blank period. Trials were randomly interleaved, and each image repeated 10 times. We hypothesize that both object identity and numerosity can be read out from the IT population activity, even when monkeys do not explicitly perform a behavioral task. We recorded from 192 neural sites, with 99 sites showing significant visual responses. We quantified the evoked neural response as the mean firing rate between a 70-170 ms window post image-onset. Preliminary results show that both object identity and its numerosity can be accurately decoded from IT population activity. Using cross-validated linear SVMs for each object type, we achieved an average decoding accuracy of 0.83±0.06 (chance=0.5). Additionally, the numerosity of each object type (0-3), decoded using a linear regression model, achieved a cross-validated accuracy of 0.78±0.02 (chance=0.25). A key feature of multiple object perception is the ability to identify an object irrespective of the other objects presented. To assess this ability, we trained a linear classifier to detect a Target object in the presence of all but one of the distractors and estimated the accuracy of this decoder when the held-out distractor was paired with the Target object. These classifiers achieve an average decoding accuracy of 0.60±0.03 (chance = 0.5) on the held-out images with novel combinations. This suggests that the IT representations facilitate the recognition of individual objects within the novel context of other objects. Future work will incorporate behavioral tasks requiring monkeys to identify and count objects, directly linking neural representations to behavior. Our findings underscore the crucial role of IT representations in the readout of multiple object relevant task information in varied behavioral contexts.

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Title: Hierarchical neural circuit implementing the reliability-based integration of 3D visual cues

Authors: *A. ROSENBERG[1], T.-Y. CHANG[2], Z. ZHU[3], R. DOUDLAH[4], A. SUNKARA[5], B. KIM[6];
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Abstract: Interacting with objects in a three-dimensional (3D) environment requires the visual system to estimate 3D object pose (position and orientation) from a pair of two-dimensional retinal projections. For primates, both perspective and stereoscopic cues support 3D vision and are perceptually integrated to produce statistically near-optimal 3D pose estimates. However, the neural circuit implementing this process has not been identified. To investigate this, we trained macaque monkeys to perform an eight-alternative forced choice tilt discrimination task in which they reported which side of a planar surface was nearest to them (i.e., tilt). The surfaces were defined by random-dot patterns and the 3D orientation was signaled by stereoscopic cues, perspective cues, or both cues (combined-cue). To investigate how these cues are represented and integrated, two viewing conditions were chosen which varied the monkeys' relative sensitivity to the perspective and stereoscopic cues. In the perspective dominant condition, surfaces were presented at a further distance and larger slant (greater depth variation across the surface). In the stereoscopic dominant condition, they were presented at a closer distance and smaller slant. Extracellular recordings were performed in area V3A and the caudal intraparietal (CIP) area during the tilt discrimination task. We found that neurons which were selective for either perspective or stereoscopic cues only were significantly more prevalent in V3A than CIP. In contrast, CIP neurons were more often selective for both cues. For neurons that were tuned for both cues, the perspective and stereoscopic cue tilt preferences were generally similar. Moreover, their tilt selectivity was greater when the two cues were presented together than individually, indicative of cue integration. Their responses to combined-cue stimuli were additionally well-described by the weighted linear sum of their responses to the individual cues. Notably, the neuronal integration weights changed dynamically with the viewing conditions such that the more reliable cue received greater weight. The observed weights also closely matched those that maximized Fisher information. These findings collectively reveal near-optimal, trial-by-trial reliability-dependent neuronal cue integration. Consistent with theoretical models of cue

integration, the results of these experiments imply a hierarchical cortical circuit which first computes separate 3D pose estimates from different visual cues and then integrates them to create a more robust representation of the external world.

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Poster

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iBehave initiative

Title: Broadening perception: Broadband visual stimuli improve neuronal representation and sensory perception in mice.

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Abstract: Natural scenes are composed of complex distributions of visual features that drive neural response patterns and shape visual perception. However, while much is known about neuronal preferences for individual visual features like orientations, we still lack insight into how broader or mixed distributions of features affect neural processing. To address this, we presented broadband visual stimuli with parametrically-controlled bandwidth of stimulus orientations and spatial frequencies to awake mice while recording neuronal population activity in the layer 2/3 of the primary visual cortex (V1) with two-photon imaging. We found that increasing the orientation bandwidth of the visual stimulus to match more closely to the orientation distribution of natural images leads to a significant increase in both the number of responding V1 neurons as

well as the strength of their responses. As revealed by our theoretical model and further backed up by additional 2-Photon experiments, this effect couldn't be solely attributed to the orientation preferences of V1 neurons; instead, it was linked to a reduction in center-surround suppression. This was more prominent for broadband orientation where image analysis also showed reduced spatial predictability. Moreover, our high-density electrophysiology experiments demonstrated that neurons in deeper layers of V1 and the superior colliculus also responded more strongly to broadband stimuli, especially when mixing broadband orientation and broadband spatial frequency stimuli. Additionally, increasing orientation bandwidth improved the ability of V1 neurons to differentiate between different spatial frequencies, which corresponds to the enhanced discrimination performance that mice showed in a visual discrimination task. Overall, our findings strongly suggest that perception of natural scenes benefits from surround modulation of spatially incoherent cues.

Disclosures: E. Balla: None. **G. Nabbefeld:** None. **C. Wiesbrock:** None. **J. Linde:** None. **P.S. Graff:** None. **S. Musall:** None. **B.M. Kampa:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.20/H12

Topic: D.06. Vision

Title: Layer-specific spatiotemporal dynamics of feedforward and feedback signals in visual object perception

Authors: *T. CARRICARTE[1], S. XIE[1], J. SINGER[1], R. TRAMPEL[2], L. HUBER[3], N. WEISKOPF[2], R. CICHY[1];
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Abstract: Human vision depends on both sensory feedforward and modulatory feedback signals emerging with complex temporal dynamics in distinct anatomical connections across the visual hierarchy. Previous studies have dissected feedforward and feedback signals based on the anatomical connection specificity in space: feedforward signals target middle cortical layers, whereas feedforward signals target deep and superficial layers. However, the temporal dynamics of feedforward and feedback information flow as present in cortical layers remain incompletely characterized.
To investigate, we applied representational similarity analysis to time-resolved electroencephalography data (N=32) and lamina-resolved fMRI data (N=10) recorded at 7T from the early visual cortex (EVC) and the lateral occipital complex (LOC) while participants viewed the same set of twenty-four different naturalistic object images. By linking the object representations across cortical layers from fMRI and time from EEG using representational EEG-fMRI fusion, we resolved feedforward and feedback signals in space and time

simultaneously. We assessed significance using cluster-based permutation statistics ($p < 0.05$ cluster definition threshold, $p < 0.05$ cluster threshold).
We found that visual representations emerged across layers within EVC around 90 - 130 ms, followed by a later stage at 160 - 190 ms during which representations were present only in the middle and superficial layers. Conversely, in LOC, we observed representations emerging in the middle layer around 150 - 170 ms, followed by a later stage at 270 - 500 ms with representations present only in the superficial layer. This suggests distinctive spatiotemporal processing patterns of feedforward and feedback along the visual hierarchy: while feedforward signals emerges early in the processing cascade across the cortical ribbon in EVC and in the middle layer within LOC, feedback signals emerge later in superficial layers in both EVC and LOC. Together, our findings characterize how the spatiotemporal dynamics of feedforward and feedback information flow orchestrate visual object perception.

Disclosures: T. Carricarte: None. **S. Xie:** None. **J. Singer:** None. **R. Trampel:** None. **L. Huber:** None. **N. Weiskopf:** None. **R. Cichy:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.21/H13

Topic: D.06. Vision

Title: Investigating the Role of Spatial Frequency in N300 Amplitude

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Abstract: The N300 has been shown to exhibit a smaller amplitude in response to “good” exemplars compared to “bad” exemplars of natural scene categories, potentially due to good exemplars having a higher degree of match with internal predictions (Kumar et al., 2021). The present study aims to understand what information is important for this prediction matching process by examining responses to good and bad scene exemplars with differing frequency content. Low spatial frequencies (LSF) carry coarse information that reveals the global shape of a scene, while high spatial frequencies (HSF) carry the detailed features of a scene. According to the frame-and-fill process, in which the visual system initially generates a prediction (a frame) and then compares it against a more detailed representation via feedback, coarse information carried by LSF via the magnocellular pathway is processed prior to fine information carried by HSF (Hochstein and Ahissar, 2002; Bar et al., 2006; Peyrin et al., 2010). To investigate if the N300 effect to good and bad scene exemplars persists in these filtered images, we conducted two electroencephalography experiments wherein we presented participants with good and bad greyscale exemplars of four natural scene categories (i.e., mountain, city, beach, and highway). In Experiment 1, participants were presented with unfiltered and low pass filtered greyscale

images and were instructed to respond on a scale of 1 to 4 how much they liked the scene. We found that the bad exemplars elicited a larger N300 than good exemplars for both the LSF and unfiltered scenes. Moreover, the difference between good and bad exemplars was comparable across unfiltered and LSF scenes, indicating that LSF information alone can drive the N300 good/bad effect. In Experiment 2, participants were shown alternating blocks of high and low pass filtered scenes and were tasked with categorizing them into one of the four categories. Although we observed an overall smaller N300 amplitude to high pass filtered scenes, the N300 good/bad effect was comparable to that observed in low pass filtered scenes. Taken together, these results show that both LSF and HSF information contributes to the prediction process that produces N300 good/bad effects.

Disclosures: L. Chong: None. **Y. Wang:** None. **K.D. Federmeier:** None. **D.M. Beck:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.22/Web Only

Topic: D.06. Vision

Support: CRC-2021-00326

Title: Neural predictivity of artificial neural networks of the primate ventral stream is significantly affected by behavioral task states

Authors: *E. FIDE[1], S. R. ROSENBAUM[2], K. KAR[3];
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Abstract: Specific artificial neural networks (ANNs) are currently the best approximation of primate ventral visual stream responses. However, it is relatively unknown how the neural predictivity of these models depends on the behavioral task state of the animals. To investigate this, we recorded neural activity across the inferior temporal (IT) cortex of two macaque monkeys (288 sites in each monkey) during a passive fixation task and a battery of active binary object discrimination tasks involving 10 objects (132 images per object). We used several high-performing ANNs (VGG-16, VGG-19, AlexNet, and ResNet-18) to predict the neural responses in the 70-170 ms time window of the IT cortex, which has been shown to best explain human behavioral patterns (Majaj et al., 2015). Given the extensive object recognition-based task training of these networks, we initially expected that they would better predict neurons when recorded during the task conditions. Interestingly, our results revealed the opposite. We observed significantly higher neural predictivity of ANNs for passive compared to active task states (VGG-16: $\%\Delta$(Passive - Active)/Passive= 12.31%, $t(231)=7.84$, $p<0.001$, pooled across monkeys). Based on previous findings (Kar et al., 2019), we hypothesized that late-phase (150-210 ms) IT responses, which are likely more affected by recurrent computations, might

exclusively account for the differences observed in IT predictivity. Indeed, further analysis confirmed that task-dependent differences are primarily driven by activity in the late (150-210 ms) time window (%Δ (Passive - Active)/ Passive= 25.64%, $t(406)=8.43$, $p<0.001$) compared to earlier (80-130 ms) ones (%Δ (Passive - Active)/Passive= 0.22%, $t(236)=-0.0062$, $p=0.99$), with the late-phase responses showing a more pronounced difference between task states. Our results provide further evidence of recurrent processing in shaping the late-phase IT responses during object recognition tasks. Importantly, these findings demonstrate that the IT predictivity of ANNs is dependent both on task demands and the phase of the IT response with respect to image onset -- symptomatic of specific computational deficits in the models (e.g., lack of feedback or recurrent processing). Therefore, we infer that behavioral task-related factors need to be considered when comparing ANNs to brain responses.

Disclosures: E. Fide: None. **S.R. Rosenbaum:** None. **K. Kar:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR346.23/H15

Topic: D.06. Vision

Support: National Science and Technology Innovation 2030 Major Program (2021ZD0203703)

Title: Rapid learning of visual categorization of abstract object concepts by macaque monkeys

Authors: *H. ZHANG, Z. ZHENG, J. HU, Q. WANG, M. XU, Z. LI, G. OKAZAWA; Inst. of Neurosci., Chinese Acad. of Sci., Shanghai, China

Abstract: Humans typically classify perceived visual objects into basic-level categories, such as dogs and cats, but they can also classify objects based on more abstract concepts (i.e., superordinate categories) such as animate, natural, and artificial. Macaque monkeys have been used as an animal model of visual object recognition, but it is unclear whether monkeys are also capable of classifying objects at this abstract level, because, unlike basic-level categories, these superordinate categories appear to lack shared image features across exemplars. Here, we developed a novel behavioral task to examine monkeys' capacity to perform such classification. We created a version of the binary decision-making task using a touchscreen system installed on the monkey's home cage. In each trial, an object image and two target boxes were shown on the screen, and the monkey had to move the object to one of the two boxes according to a hidden categorization rule learned through reward feedback. Using this task design, we tested monkeys with various categorization tasks defined by rules humans would use to classify objects at an abstract level, such as animate vs. inanimate, natural vs. artificial objects, and mammal vs. non-mammal animals. Each task contained around 80 training images and a similar number of new images to test generalization. We found that monkeys could learn those tasks (80-90% correct

for training images) within 2-3 days (700-800 trials per day) and generalize the learned rules to new images (~80% correct). We further tested monkeys' categorization behavior with larger image sets (~ 3500 images) selected from the THINGS database (Hebart et al., 2019; Stoinski et al., 2023). Again, monkeys performed well on those images shown without repetitions (80-90% correct). By comparing their behavior with different visual models (V1-like model, texture model, etc.), we confirmed that low/mid-level image features could not explain monkey behavior. In contrast, high-level image features extracted from artificial neural networks could solve the task and fit monkey behavior well. Thus, features extracted from these network models are sufficient to classify objects at an abstract level. The results suggest that the primate brain is equipped with the capacity to extract features correlated with abstract visual concepts used in human language and associate them with behavioral responses.

Disclosures: H. Zhang: None. **Z. zheng:** None. **J. Hu:** None. **Q. Wang:** None. **M. Xu:** None. **Z. Li:** None. **G. Okazawa:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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Topic: D.06. Vision

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Vision Core Grant P30EY01730
Office of Research Infrastructure Programs Grant OD010425

Title: Stimulus selective prospective signals modulate responses of macaque area V4 neurons

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Abstract: In natural settings, vision is a dynamic process, with a continuously changing retinal image. Each saccade shifts the retinal reference frame, changing the image present within the receptive field (RF) of a neuron, but this consistent updating of the retinal image does not impair perceptual stability. Prospective remapping of the RF, where the spatial position of the RF shifts towards its future location (future RF: fRF) just prior to the onset of a saccade, may be involved in perceptual stability by linking pre- and post-saccadic representations of visual space. While prospective encoding of stimuli within the fRF has been previously demonstrated in V4, the precise temporal dynamics remain unclear, and it is uncertain whether prospective signals are stimulus selective. Using tungsten electrodes and high-density Neuropixels probes, we measured the responses of V4 neurons as a macaque made saccades to a target dot and stimuli were

presented in the fRF. For all experiments, RF position was determined using an automated RF mapping procedure, and for Neuropixels experiments, stimulus position was determined by the aggregate RF of all neurons recorded by the probe. In one set of experiments, we manipulated the timing of stimulus presentation relative to saccade onset to specifically probe the temporal dynamics of prospective encoding. In another set of experiments, we manipulated stimulus identity at the time of saccade onset to probe the effects of stimulus selectivity. Across 12 sessions of Neuropixels experiments (1699 recorded neurons), and 34 sessions of single-unit experiments, we observed changes both in the pre- and post-saccadic response dynamics that were associated with the prospective encoding of stimuli. Specifically, 11% of neurons showed responses during the saccade planning period that were not selective for the stimulus within the fRF, while 31% of neurons showed stronger responses on trials that included a perisaccadic change in stimulus identity. These results suggest that stimulus selective prospective encoding in V4 may play a role in signaling discontinuities in perceptual stability.

Disclosures: R.S. Kamath: None. **T. Kim:** None. **A. Pasupathy:** None.

Poster

PSTR346: Category-Specific Visual Processing in Human and Nonhuman Primates

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Topic: D.06. Vision

Support: NIH grant EY035005
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Title: Hierarchical computation of 3D visual representations across macaque V3A and CIP

Authors: *R. DOUDLAH[1], L. KRESSER[2], T.-Y. CHANG[3], B. KIM[4], A. SUNKARA[5], A. ROSENBERG[6];
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Abstract: As we use our eyes to visually explore an environment, the retinal projections of the scene vary greatly with the gaze position. Despite this volatility of the retinal images, the scene is perceived as stable. We previously showed that a high-level representation of three-dimensional (3D) surface pose (position and orientation) is hierarchically constructed across macaque area V3A and the caudal intraparietal (CIP) area. In that work, eye position was held at a constant location in space while planar surfaces were presented at different distances. Here we test whether vergence eye position signals are utilized within this pathway to create 3D visual

representations that are tolerant to the gaze distance, achieving 3D visual stability. In both areas, we identified neurons whose responses were selectively tuned for vergence angle during the fixation of a small visual target. To disentangle low-level visual feature selectivity from high-level 3D pose selectivity, we measured 3D surface orientation tuning at a single distance but with multiple fixation distances (in front of, at, or behind the surfaces). Depending on the fixation distance (vergence angle), the binocular disparities defining the surfaces were either all far, equal proportions of far and near, or all near. We found that 3D surface orientation tuning was more tolerant to the fixation distance in CIP than V3A, implying that 3D visual representations which are tolerant to the vagaries of eye movements are hierarchically computed along this pathway. We present a model that synthesizes our earlier empirical results on the visual computations implemented across V3A and CIP with the present results on the role of vergence signals in achieving 3D visual stability. In this model, the output of units which encode local absolute disparities are selectively integrated to compute absolute disparity gradients. These gradient-selective responses are then gain modulated by vergence signals modeled after the empirically measured vergence tuning curves. By selectively integrating the output of joint disparity gradient and vergence selective units, downstream units achieve high-level 3D pose selectivity that is tolerant to the gaze distance. These results collectively reveal that computations implemented across the V3A-to-CIP hierarchy produce stable visual representations that can support perception and action in a 3D world.

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Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.01/H18

Topic: E.02. Cerebellum

Support: NIH Grant DC016905
Hearing Health Foundation
National Ataxia Foundation
NIH Grant DC021671

Title: Developmental regulation of NMDA receptors in cerebellar unipolar brush cells

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Abstract: Unipolar brush cells (UBCs) are excitatory interneurons that have a characteristic single dendritic brush that amplifies and extends incoming sensory signals in the cerebellum. UBCs transform synaptic input through their ionotropic and metabotropic glutamate receptors. Differential regulation of receptors is a critical cell-type specific developmental process. For

example, another excitatory cerebellar interneuron, the granule cell, expresses the NMDA receptor NR2B/A subunits in early postnatal life that are replaced by NR2C subunits in adulthood. NR2C subunits are less sensitive to Mg^{2+} block and have different kinetic properties, resulting in markedly different granule cell synaptic responses across development. How UBCs regulate glutamatergic receptors through development is not understood. We aim to examine how UBCs regulate NMDA receptor subunits during maturation and whether signaling through these receptors is necessary for normal UBC structure and function. We conducted whole-cell patch clamp electrophysiology recordings from UBCs in acute brain slices to characterize NMDA receptor-mediated currents in young (P10-14) and electrophysiologically mature (P26-32) mice. Our results show the presence of NMDA receptor-mediated currents at resting membrane potential in young, but not mature, UBCs, which are abolished by NR2C/D specific antagonists. This suggesting that young UBCs express NR2C/D subunits, which are lost later in development. Fluorescence in situ hybridization using RNAscope will be used to confirm the presence of NR2C/D RNA transcripts in young UBCs. Further experiments will investigate the role of NMDA receptors in (1) migration of UBCs, (2) UBC brush development, and (3) temporal integration of synaptic signals at the mossy fiber-UBC synapse. This study will provide novel insights into the role of NMDA receptors in UBC development and cerebellar circuit processing.

Disclosures: H.N. Hariani: None. **T. Balmer:** None.

Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

Location: MCP Hall A

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Program #/Poster #: PSTR347.02/H19

Topic: E.02. Cerebellum

Support: NIH Grant R21NS124217
NIH Grant F31NS129256

Title: Comparative morphology of cerebellar Purkinje cells reveals an evolutionary trajectory of enhanced dendritic complexity in humans

Authors: *S. E. BUSCH[1], A. FERRELL[1], M. HILLEGAS[2], W. D. HOPKINS[3], C. C. SHERWOOD[2], C. HANSEL[1];
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Abstract: Cerebellar Purkinje cell (PC) dendrites conduct robust supervised learning that is highly conserved across vertebrates but also serves numerous species-specific behaviors. We recently found that morphology shapes the complex integrative capacity of these cells; mouse

PCs with multiple primary dendrites can, non-canonically, host multiple climbing fiber (CF) inputs (Busch & Hansel 2023, *Science*). Regional variation in PC structure demographics provided early support of the hypothesis that morphology-dependent cellular function may underlie task-specific regional computations. Our finding that human PC demographics also vary by region, are almost universally multi-dendritic, and have more proximal branching may supply added support. But factors like allometry or foliation are plausible confounds as it is unclear if these traits are unique to humans, present across primates, or depend on brain size. To comprehensively analyze PC morphology with respect to phylogeny, allometry, and foliation, we immunolabeled PCs (calbindin) in adult primates (monkeys, lesser and great apes, human) and non-primates (mouse, elephant). We used high resolution confocal imaging to 1) produce the most complete digital reconstructions of human (and other primate) PCs ever recorded, and 2) measure population structural demographics by region and species. The reconstructions reveal large differences-of scale and kind-between species, possibly indicating distinct cellular computational capacities. Compared to mouse, human PCs (>P80,45yo; n=5,5) are 11x longer-yet non-primary dendrites are equally thin-and more horizontally ramified at angles of ~20° vs ~40°. With similar spine densities of 4-10/um (higher distally), we can extrapolate that human cells may harbor a staggering 0.5-1 million spines (25-50,000 in mice). Co-labeling putative CFs (peripherin) in human shows common multi-innervation. In primate PC populations, the rate of multi-dendrite or horizontally ramified categories both increase with phylogenetic proximity to human (n>200 cells/species). Echoing this, soma-to-bifurcation distance drops linearly: macaque > gibbon > gorilla > chimpanzee > bonobo > human. The elephant demographic profile is distinct from the primate trend, with more multi-dendritic but far fewer horizontal PCs than human. Thus, phylogenetic proximity to humans-and not allometry-strongly predicts more proximal and segregated multi-dendrite structure. This work unveils extensive anatomical diversity in a brain region considered evolutionarily stereotypical and supports the hypothesis that PC morphology underlies functional specificity by region and species.

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Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

Location: MCP Hall A

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Program #/Poster #: PSTR347.03/H20

Topic: E.02. Cerebellum

Support: K-Brain Project RS-2023-00266872

Title: Serotonergic Regulation of Fastigial Nucleus for Muscle Activity Regulation

Authors: *Y. BAK[1], S. LEE[2], J. LEE[3], Y. LEE[1], J. JEONG[4], D. KIM[5];
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Abstract: Title: Serotonergic Regulation of Fastigial Nucleus for Muscle Activity Regulation Authors: Yenah Bak, Sinjeong Lee, Junesu Lee, Ye Won Lee, Jiwoo Jeong, Daesoo Kim Abstract: Increased activity in the deep cerebellar nucleus (DCN)-projecting dorsal raphe nucleus has been reported to be associated with dystonia, a movement disorder caused by involuntary muscle contraction in mouse (Kim et al., 2021), and serotonin activity in the DCN has been linked to enhanced motor ability in rats (Zhang et al., 2014). These findings indicate the possibility of the role of serotonergic regulation, mainly from the dorsal raphe nucleus (DRN), on the DCN for muscle regulation. However, the connection between serotonergic activity and DCN for muscle regulation is still unclear. We used chemo-genetic and pharmacological methods to observe the behavioral changes and muscle activity via serotonin receptors in wild-type mouse-line. We found that activation of serotonergic neurons from DRN at DCN gradually increased muscle tension and resulted in muscle co-contraction episodes. Further, suppressed neuron activity in the DCN altered gait patterns. Together, these results support that serotonin from the DRN can regulate muscle activity through DCN and provides insight for the role of neuromodulator regulation on motor functions.

Disclosures: Y. Bak: None. **S. Lee:** None. **J. Lee:** None. **Y. Lee:** None. **J. Jeong:** None. **D. Kim:** None.

Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.04/H21

Topic: E.02. Cerebellum

Support: FRM EQU202003010555
ANR 21 CE16 0036 01
ANR-19-CE16-0019-02

Title: The heterogeneity of synaptic strength and short-term plasticity is a canonical yet tunable property of the input layer of the cerebellar cortex

Authors: *S. BORDA BOSSANA[1], B. SERMET[2], F. BENDER[1], A. BARRI[1], D. A. DIGREGORIO[3];
[1]Inst. Pasteur, Paris, France; [2]Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [3]Physiol. and Biophysics, CU Sch. of Medicine, Anschutz Sch. of Med., Aurora, CO

Abstract: The cerebellum is thought to use canonical circuitry and similar computations across its subregions to perform adaptive learning to fine-tune the neural activity driving behavior. Because the timescales of the behavior can vary, it has been proposed that the temporal dynamics of learning can vary in different cerebellar regions. To perform these computations efficiently,

we hypothesize that a diversity of granule cell (GC) activity patterns is required. However, it remains to be determined whether other functional properties are tuned in a regionally specific manner to accommodate the temporal diversity of neural dynamics underlying different behaviors. In the cerebellar Lobe X, we previously showed that short-term synaptic plasticity (STP) between mossy-fiber (MFs) and GCs is diverse and leads to different delays to the first spike. Subsequent theoretical work has demonstrated that STP heterogeneity is sufficient to generate a rich diversity of cerebellar granule cell firing patterns, which mediates temporal learning. Moreover, the model predicts that the time scales of STP influence the time scales of learning. In response to an instantaneous, persistent stimulus, the time course of the synaptic conductance amplitude can be described by a characteristic time constant (tau_{syn}). Tau_{syn} is proportional to the inverse vesicle refilling rate and inversely proportional to the MF firing rate and release probability of the synaptic vesicles. Here, we set out to use patch-clamp electrophysiology to estimate synaptic diversity and STP time scales in three different regions of the cerebellum (Lobe X, Crus1, and Simplex). We found that synaptic conductance amplitude and STP are heterogeneous in all regions. This supports the hypothesis that functional synaptic diversity at the input layer is a canonical feature throughout the cerebellum. However, the time scales of STP did vary between Crus1 and Simplex. Slower plasticity time scales in Simplex GCs are consistent with slower and longer whisker air puff-evoked calcium responses in vivo compared to Crus1 GCs. Thus, our results suggest that the timescales of synaptic plasticity may be tuned to the bandwidth demands of the underlying behavior of neural circuit dynamics.

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Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

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Program #/Poster #: PSTR347.05/H22

Topic: E.02. Cerebellum

Support: NS123933
NS131652

Title: Endocannabinoid signalling is altered in murine models of Duchenne Muscular Dystrophy

Authors: *S. MITRA[1], E. AVERYT[2], J. R. PUGH[3];
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Abstract: Duchenne Muscular Dystrophy (DMD) is an X-linked genetic condition primarily characterized by progressive skeletal muscle degeneration. However, DMD patients also exhibit impaired cognitive function and high comorbidities with neurodevelopmental disorders, such as

ADHD and autism. Further, dystrophin, the protein responsible for DMD, is expressed in select CNS neurons, with the highest expression in cerebellar Purkinje cells (PCs). While consequences of dystrophin loss in muscle tissue have been studied extensively, the mechanisms of CNS disfunction are still unclear. Previous work shows that dystrophin is localized to inhibitory synapses in PCs and loss of dystrophin results in reduced number and function of these synapses. However, recent studies have demonstrated significant changes in endocannabinoid (EC) signalling in dystrophic muscle, prompting us to examine EC signalling in the cerebellum of dystrophin deficient mice. ECs are critical for short- and long-term synaptic plasticity and proper circuit function in the cerebellum. EC signalling was measured by patch clamp electrophysiology in acute cerebellar slices from young adult (P30-P50) WT and *mdx* (a common model of DMD lacking dystrophin) mice. We first measured depolarization induced suppression of excitation (DSE, a CB1 receptor-dependent form of short-term plasticity) at parallel fiber (PF)-PC synapses to assess presynaptic CB1 receptor function. We find robust DSE induction at PF-PC synapses in WT mice (78.9±16.1% of baseline) but little or no DSE in *mdx* mice (94.5±6.2% of baseline, p=0.036). We also measured induction of CB1 receptor-dependent LTD (using 100 Hz PF stim. paired with PC depolarization) at PF-PC synapses. We find that LTD induction was reduced or absent in *mdx* mice (98.8±4.4%) compared to WT mice (78.3±8.8%; p=.023). These data suggest that EC signalling through CB1 receptors is significantly reduced in *mdx* PCs. In order to more specifically investigate cellular changes due to loss of dystrophin only in PCs, we crossed the DMD^{COIN} mouse line recently developed in our lab with a PCP2-Cre line (a PC specific Cre). Immunolabelling in these mice show loss of dystrophin in PC, but no change in expression in muscle. Further, PCP2:DMD PC show reduced inhibitory synapses number and efficacy, similar to *mdx* mice. In these mice, we find that DSE at PF-PC synapses is absent (98.3±4.7%), similar to results from *mdx* mice. These data suggest EC function in cerebellum is impaired by loss of dystrophin in PC, potentially contributing to cognitive and motor impairments associated with DMD. Further, the EC may be a promising target for treatment of CNS-related deficits in DMD.

Disclosures: S. Mitra: None. **E. Averyt:** None. **J.R. Pugh:** None.

Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR347.06/H23

Topic: E.02. Cerebellum

Support: NIH Grant to KK R01DA044761
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Title: Mechanisms of ethanol-induced motor attacks in a mouse model of episodic ataxia type 2

Authors: *J. O. TINDI[1], A. VITENZON[2], H. D. SNELL[3], L. SPAETH[4], K. KHODAKHAH[5]; [1]Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY; [2]Life Edit

Therapeut., Durham, NC; [3]Yale Univ., New Haven, CT; [4]Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med. Dominick P. Purpura Dept. of Neurosci., Bronx, NY; [5]Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med. Postdoc Dominick P. Purpura Dept. of Neurosci., Bronx, NY

Abstract: Ethanol is the most abused substance worldwide with wide-ranging neurobehavioral consequences. However, it's mechanism of action is not understood. Episodic ataxia type 2 (EA2) is a condition characterized by periods of severe and debilitating ataxia and dyskinesia (attacks) that can be triggered by stress, caffeine, or ethanol. EA2 is caused by loss of function mutations in the CACNA1A gene that encodes the pore-forming α subunit of the P/Q-type voltage gated calcium channel. Previous work using the *tottering* mouse model of EA2 has shown that dysfunction of cerebellar Purkinje cells is both necessary and sufficient for triggers to induce motor attacks. Moreover, it has recently been shown that stress-induced attacks in *tottering* mice are due to noradrenergic modulation of cerebellar Purkinje cell firing via Casein Kinase 2 (CK2) and phosphocalmodulin-dependent regulation of small conductance calcium-activated potassium channels. Here we examined the mechanism of ethanol-induced attacks and whether CK2 was also required. Similar to stress, we discovered that shRNA-mediated knockdown of CK2 in the cerebellum prevents ethanol-induced motor attacks in *tottering* mice as well. In an *in vitro* kinase assay we found that ethanol does not significantly affect recombinant CK2 activity, suggesting ethanol does not directly (physically) interact with CK2. Metabolism of ethanol was also not required as inhibition of aldehyde dehydrogenase failed to prevent attacks. Previous work has shown that low millimolar concentrations of ethanol can increase tonic inhibition in the cerebellum that is mediated by δ subunit-containing $GABA_A$ receptors (δ-$GABA_A$Rs) via a mechanism that relies on inhibition of nitric oxide synthase (nNOS). However, we found that neither the δ-$GABA_A$Rs agonist THIP, nor inhibition of nNOS was sufficient to trigger motor attacks in *tottering* mice. Ethanol also inhibits α6-$GABA_A$Rs in the cerebellum, and by doing so, reduces tonic inhibition on granule cells. Consistent with this potential mode of action, we found that intracerebellar infusion of furosemide, an antagonist of α6-$GABA_A$Rs, triggers motor attacks. However, neither ethanol nor furosemide affected the intrinsic firing of Purkinje cells in acute cerebellar slices of *tottering* mice, even though the firing of Purkinje cells during ethanol-induced attacks transforms to high frequency burst firing similar to that observed during stress and caffeine-induced attacks. Further experiments will shed more light on exactly how ethanol triggers attacks in the *tottering* mice with the goal of elucidating mechanisms underlying ethanol effects in EA2, and potentially more broadly in the CNS.

Disclosures: J.O. Tindi: None. **A. Vitenzon:** None. **H.D. Snell:** None. **L. Spaeth:** None. **K. Khodakhah:** None.

Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

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Program #/Poster #: PSTR347.07/H24

Topic: E.02. Cerebellum

Support: 1R37NS128416

Title: Subnetworks of molecular layer interneurons and Purkinje cells form the output of the cerebellar cortex

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Abstract: Damage to the cerebellum results in dysmetric movements, yet the activities of individual Purkinje cells (Pcells) show little relationship to the specific kinematics of the movement. A critical clue is that the inferior olive provides a climbing fiber to each Pcell that serves not only as its teacher, but also defines an axis in space along which the Pcell is most sensitive to errors. Critically, for each Pcell this axis also defines its downstream effects on behavior: when simple spikes of a Pcell are suppressed, the result is production of force that pulls precisely along the axis of its preferred error. But how does this invariant property arise when individual Pcells have such diverse firing rates? Here, we used silicon probes to gather data simultaneously from multiple layers of the cerebellar vermis in two marmosets while they performed goal-directed saccadic eye movements (46 recording sessions). Using electrophysiological properties, we isolated and classified >3000 units into inputs (mossy fibers and climbing fibers), outputs (Pcells, 254 units), molecular layer interneurons (MLIs, 574 units) and granular layer interneurons (GLIs). Near movement onset, the mossy fibers conveyed high frequency information regarding the goal of the movement and the state of the eyes during that movement. On the other hand, the climbing fibers provided low frequency information regarding the direction of the visual target and the intended movement. We used corrected cross-correlograms between simultaneously recorded cells to form a connectivity matrix between Pcells and MLIs. The connectivity matrix revealed that Pcells and MLIs formed small cliques of interconnected cells, sharing similar climbing fiber responses (88 recorded cliques). While Pcells included bursters and pausers, the MLIs predominantly exhibited a burst during the movement. Despite the diversity of Pcell firing rates, when we projected their responses on their preferred error axis, the result was a largely invariant pattern of simple spikes that encoded movement kinematics. Remarkably, when the activities of the MLIs within the clique were projected onto the same error axis, the MLIs exhibited a response that mirrored the Pcell response. In summary, our results suggest that the climbing fibers organize specific groups of Pcells and MLIs into a clique of synchronous spiking units that control the movement along a single axis: the preferred axis of error signaled by the climbing fibers.

Disclosures: M. Fakharian: None. **A. Shoup:** None. **P. Hage:** None. **J. Pi:** None. **R. Shadmehr:** None.

Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

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Topic: E.02. Cerebellum

Support: NIH Grant NS122741

Title: Cerebellar transcranial electrical stimulation produces a frequency-dependent bimodal cerebellar output pattern.

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[2]Biomed. Engin., New Jersey Inst. of Technol., Newark, NJ

Abstract: Accumulating anatomical, clinical, and imaging evidence indicates that the cerebellum has central roles in motor and cognitive functions, and that cerebellar dysfunction impacts these functions. Several lines of evidence suggest that Cerebellar Transcranial Electrical Stimulation (ctES) improves motor learning and cognitive and emotional processes in normal and brain-injured individuals. Thus, ctES has the potential to be an appealing, non-invasive treatment option for psychiatric and neurological disorders. However, its potential has been limited by the significant knowledge gap that exists on how electrical stimulation alters cerebellar output to produce its benefits at the cellular and circuit levels. Moreover, at the single-cell level, this issue has only been studied using direct brain surface stimulation, and in ctES, the stimulation is applied from outside of the skull, whose properties likely alter the electric field induced by ctES within the cerebellum. As a result, the effects of ctES on cerebellar activity are largely unknown. Thus, we investigated this issue by making single-unit recordings of Purkinje cells (PC) and cerebellar nuclear (CN) cells in response to ctES in anesthetized adult female Sprague-Dawley rats. The ctES electrode was positioned on the skull above crus 1, either ipsilaterally just medial to the recording site or contralaterally. The return electrode was placed under the skin of the shoulder ipsilateral to the recorded cell. The entrainment of spike activity was recorded for frequencies ranging from 0.5 to 80 Hz. We found ctES can strongly modulate both PC and CN activity in a frequency-dependent manner. An unimodal response was seen for PCs, whereas CN cells exhibited both uni- and bi-modal patterns. We applied model-based clustering for circular data to fit a mixture of two von Mises populations to the bimodal distributions to separate the bimodal response into two unimodal responses that could be separately analyzed. The strength of PC and CN entrainment increased with stimulation frequency, as measured by the mean circular vector amplitude. The phases of PC and CN vectors suggest that CN responses are due to the modulated PC activity rather than a direct polarization of the CN cells. The nearer ctES location to the recording site produced a stronger entrainment, indicating that ctES electrode location is an important modulation parameter. The results show that transcranial stimulation can modulate cerebellar output, which has potential implications for its use in treating motor and cognitive disorders.

Disclosures: D. Mourra: None. **M. Sahin:** None. **E.J. Lang:** None.

Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

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Program #/Poster #: PSTR347.09/H26

Topic: E.02. Cerebellum

Support: 1R37 NS128416

Title: Better tools for measuring temporal coordination of spikes in the cerebellum

Authors: M. FAKHARIAN[1], P. HAGE[2], A. SHOUP[1], *R. SHADMEHR[3];
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Abstract: In the cerebellum, one neuron can influence another neuron's spike timing with millisecond precision. However, because many of the cell types are inhibitory and can synchronously burst or pause, there is controversy regarding how to measure the spike interactions, particularly during behaviors in which firing rates change greatly.
Here, we evaluate some of the leading computational techniques using ground truth data and find that while most estimators are unbiased, their uncertainty changes greatly with the firing rates of the neurons. Because of this signal-dependent variance, in a realistic scenario in which the data consists of ~1000 trials or less, all of the estimators appear unreliable.
Fortunately, we can reduce the uncertainty by increasing the estimation window: when we measure spike interactions at 1 ms resolution but compute probabilities over a window of contiguous bins, the result exponentially reduces the uncertainty of the estimator as a function of the estimation window size. This new method appears to provide a much more reliable way to measure spike interactions.
To test this approach, we apply the tools to silicon probe recordings from the marmoset cerebellum and find that the Purkinje cells (P-cells) and molecular layer interneurons (MLIs) form statistical cliques. We record the activities of the same neurons during two behaviors, saccades, and licking, and find that cells within a clique are far more synchronous than those outside the clique, and cells that are synchronous during one behavior are not necessarily synchronous during another behavior. The results present new computational tools that significantly improve the robustness of statistical measures of spike interactions among the neurons of the cerebellum.

Disclosures: M. Fakharian: None. **P. Hage:** None. **A. Shoup:** None. **R. Shadmehr:** None.

Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

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Title: Homeostatic Bidirectional Plasticity in Zebrin II +/- Micromodules

Authors: *E. FERNANDEZ SANTORO[1], A. M. BADURA[1], C. DE ZEEUW[1,2], M. NEGRELLO[1];
[1]Neurosci., Erasmus Med. Ctr., Rotterdam, Netherlands; [2]Netherlands Institute for Neuroscience, Royal Academy of Arts and Sciences, Amsterdam, Netherlands

Abstract: The Olivocerebellar system plays a central role in supervised and unsupervised motor learning, crucially contributing to the coordination, precision and accurate timing of movements. The Purkinje cell (PC) receives all incoming sensory and motor information and generates the sole output of the cerebellum. The high firing frequency (FF) of the PC (50-120Hz) allows for precise bidirectional changes in its FF to be made which facilitate cerebellar learning. The function of cerebellar micromodules —topographically organized loops of PCs, cerebellar nuclei (DCN) and inferior olive (IO) cells and a powerful excitatory feedback connection, via climbing fibers (CF)— can be determined by the specific response of their PCs to CF activity. We developed an Olivocerebellar model with two micromodules which consist of Zebrin II negative (Z^-) and Zebrin II positive (Z^+) PCs projecting to DCN cells and IO cells. With this model we study the dynamics of plasticity of this closed loop when PCs are subjected to stochastic input. This model is endowed with biophysically plausible IO cells, with both resonant and oscillatory dynamics. Our experiments inquire on the role of induced IO reverberations and electrotonic coupling on PC homeostatic synaptic plasticity (PC-PF), which is incorporated through LTD/LTP mechanisms. We look at the differences across Zebrin zones and we also attempt to gauge the contribution of conductivity of the IO gap junctions on the input dynamics of the Olivocerebellar loop. Each micromodule consists of 5 PF bundles, 100 PCs, 40 DCN cells and 40 IO cells. We find that specific frequencies that evoke a resonance in the olivary nucleus become encoded in the PC weights (at PF-PC synapse), rendering the system able to promote inputs with specific frequency components. We also find that frequency selectivity is reduced when olivary cells are decoupled. This may indicate that in the presence of strong coupling, PCs are separating temporal patterns. We find that Z^- PCs have more propensity for depression while for Z^+ PCs it is potentiation, this seems to be solely driven by the PC intrinsic FF. Particular

ranges of frequency bands bring this model closer to physiological responses, indicating that specific frequency components may control the resonance and IO synchronicity.

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Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

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Topic: E.02. Cerebellum

Support: NIH R35-NS116854
2T32MH067564

Title: Topographically distinct complex spike responses to regular and irregular trains of tactile stimuli revealed by high-speed widefield Ca imaging of Purkinje dendrites

Authors: *S. GOLDSTEIN[1], S. T. BROWN[1], I. M. RAMAN[2];
[1]Northwestern Univ., Evanston, IL; [2]Neurobio., Northwestern Univ., Evanston, IL

Abstract: The cerebellum participates in sensorimotor coordination in part by tracking sub-second time intervals between behaviorally relevant events. Here, we have investigated the extent to which absolute and/or relative time intervals between repetitive sensory stimuli are represented in complex spikes in populations of Purkinje (Pkj) cells across crus I of the cerebellar cortex. We performed high-speed (250 Hz) widefield imaging of hundreds of Pkj cell dendrites expressing the fast calcium indicator, jGCaMP8f (50% rise = ~6.6 ms; 50% decay = ~80 ms), with 4-ms temporal resolution and spatial resolution sufficient for discriminating individual, neighboring neurons. The high imaging rate and rapid indicator kinetics enabled precise calculation of the timing of complex spikes. To test how Pkj cells respond to climbing fiber inputs activated by sensory stimuli with different degrees of temporal regularity, dendrites were imaged in awake, head-fixed mice during regular and irregular trains of air puffs applied to the ipsilateral whisker pad. Regular trains had an inter-puff interval of 300 ms and irregular trains had inter-puff intervals of 100, 200, 300, 400, and 500 ms. During both protocols, dendrites generated 1-3.5 fluorescent transients per second, consistent with single unit electrophysiological recordings of complex spikes in Pkj cells. With regular stimulation, the complex spike responses of imaged Pkj cells reliably clustered into two broad categories. (1) One group of Pkj cells first showed a significant increase in complex spike firing after the puff (n = 283/405, “complex spike elevated,” CxSE), and (2) a second group first showed a significant reduction in complex spike firing after the puff (n = 63/405, “complex spike reduced,” CxSR). These subsets of Pkj cells separated into clearly delineated clusters of crus I. Since neighboring neurons shared common response profiles, these physiological responses appear likely to represent neurons receiving input from common or coupled populations of inferior olivary

neurons. With trains of irregular air puffs, the probability of complex spiking varied with inter-puff intervals. In CxSE cells, short-latency firing increased with interval duration, while in CxSR cells, long-latency firing increased with interval duration, after the initial reduction. CxSE cells thus appear to be innervated by climbing fibers (CF) that respond directly to puffs, whereas CxSR cells may be innervated by CFs that respond indirectly, possibly through electrical coupling in the inferior olive.

Disclosures: S. Goldstein: None. **S.T. Brown:** None. **I.M. Raman:** None.

Poster

PSTR347: Cerebellum: Cell Types and Circuit Physiology

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Topic: E.02. Cerebellum

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Title: Organization of excitatory and inhibitory inputs to the inferior olive

Authors: *B. ZINGG[1], H. DONG[2];
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Abstract: The inferior olive plays an important role in refining motor movements via its climbing fiber projections to the cerebellar cortex. Inputs to the olive have been described for many species using classic tracer and electrophysiological approaches, however a complete map of all sources of excitatory and inhibitory input has yet to be fully reported. Here we use monosynaptic rabies tracing in transgenic mice to directly reveal inputs to the olive from across the entire brain and spinal cord. All sources of input were examined for the presence of VGAT co-expression, a marker for inhibitory neurons. Besides the well characterized GABAergic projection from cerebellar nuclei, we identified numerous sources of long-range inhibition to the olive from mid- and hindbrain structures, many of which, to our knowledge, have yet to be described. We then cross-examine these input sources using dual-color viral co-injections in Vglut2-Cre x VGAT-Flp mice to reveal excitatory and inhibitory axon targeting to olivary subnuclei. We report distinct lateralization features for excitatory versus inhibitory targeting, describe trends in somatotopic organization, and report complete input profiles for each olivary subnucleus. This detailed map will help reveal the nature of information processed within each of the subnuclei, and more broadly, within their corresponding downstream cerebellar targets.

Disclosures: B. Zingg: None. **H. Dong:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

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Topic: E.04. Voluntary Movements

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DARPA L2M Program W911NF1820264
Division of Biokinesiology 290 and Physical Therapy Graduate Teaching Assistantships

Title: Vestibular output is also gated by voluntary action of the arm

Authors: *A. BARTSCH[1], S. CHENG[2], Y. ALVI[2], F. J. VALERO-CUEVAS[2];
[1]Biokinesiology and Physical Therapy, USC, Los Angeles, CA; [2]Alfred E. Mann Dept. of Biomed. Engin., USC, Los Angeles, CA

Abstract: The vestibular system is among the oldest and most fundamental contributors to motor behavior as it is critical to maintaining posture and balance. However, such low-level signals could interfere with cortically-mediated voluntary behavior that naturally affects posture and balance. Consequently, it has been proposed that vestibular output is 'gated' (dubbed vestibular suppression) to avoid undesirable self-perturbations during voluntary head movements and locomotion. Here we demonstrate such gating also occurs for voluntary arm function. We tested sixteen unimpaired young adults (mean age: 19.2, range: 18-27 years old) under three seated tasks: rest, isometric contraction, and voluntary reaching movement with their right arm. EMG signals were recorded from upper extremity and neck muscles: Biceps (Bic) and Triceps Brachii(Tri), Anterior (ADelt), Middle (MDelt) and Posterior (PDelt) Heads of Deltoid, Upper Trapezius (UTrap), and Sternocleidomastoid (SCM). The strength of our evidence comes from comparing coherence at baseline (No Stimulation) and after either Sham or Galvanic Vestibular Stimulation (GVS). Our results show clear patterns of reduced pair-wise Intermuscular Coherence between specific neck muscles during visual tracking at rest and during voluntary arm isometric contractions and reaching movements. Specifically, the coherence between neck muscles (SCM-UTrap) seen at rest increased when GVS was applied, but it was suppressed when their gaze was fixed on a screen. Moreover, this increased coherence in neck muscles was also suppressed during voluntary isometric contractions and reaching movements even when GVS was applied. Thus, these findings extend vestibular suppression to voluntary arm function. On the other hand, no changes were found in pairwise intermuscular coherence during Sham (compared with No stimulation) or in arm muscles at either rest or during voluntary movement during GVS in these neurotypical adults. Consequently, this confirms the common (yet unproven to our knowledge) notion that arm muscles do not receive vestibular neural drive. In addition to shedding light on the mechanisms that mediate competing descending outputs for voluntary function, this work also serves as a baseline against which to compare potential task-dependent dysregulation of vestibular-mediated output to the neck and arms in stroke and neurological conditions.

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Poster

PSTR348: Sensory Processing in Motor Control

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Topic: E.04. Voluntary Movements

Support: NSERC Grant 2017-04504
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Title: The effects of agonist and antagonist muscle tendon vibration on kinesthetic targeting tasks

Authors: *G. ESCHELMULLER, J. ZHANG, A. SZARKA, N. BUTLER, H. E. KIM, J. INGLIS, R. CHUA;
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Tendon vibration of a lengthening muscle produces the kinesthetic illusion of increased muscle length, leading to undershooting during target-directed reaching[1]. Dual agonist/antagonist vibration may degrade proprioception[2]; however, it is unclear how it would affect performance in a target-directed movement task. The primary purpose of the current study was to investigate the effects of agonist, antagonist, and dual vibration on a kinesthetic targeting task. We hypothesized that antagonist vibration would produce a bias in end point, agonist vibration would produce no effect, and dual vibration would produce no bias but an increase in variability. Previous research has focused on single-joint movements; thus, our secondary purpose was to examine the effects of vibration on one and two-dimensional movements. Participants (n=30) either performed a one-dimensional (elbow extension) or a two-dimensional (wrist motion in flexion/extension and adduction/abduction) movement to a visual target(s). Participants completed these movements with flexor, extensor, dual flexor/extensor, and no vibration. In the elbow-extension task, flexor vibration produced an undershooting effect, while extensor vibration produced an overshooting effect. The effect in the two-dimensional task was not as simple, as each muscle may act as the agonist or antagonist to varying degrees depending on the target location. Overall, the illusions were largest when the muscle was acting as the antagonist (lengthening) and disappeared when the muscle was acting as the agonist (shortening). Interestingly, in both tasks there was no change in error variability with dual vibration, indicating it did not degrade proprioception. We hypothesize that the effects of tendon vibration depend on the reliability of the afferent information coming from the muscle. When the muscle is being lengthened (stretches muscle spindles), the afferent signal is more reliable, and therefore, vibration produces robust kinesthetic illusions. When the muscle is being rapidly shortened (unloads muscle spindles), the afferent signal is less reliable, resulting in no kinesthetic illusion. In the case of our elbow-extension task, the movement was slow enough that the agonist was likely not fully unloaded, resulting in a small illusion. Overall, our results demonstrate that vibration-induced kinesthetic illusions can be used to perturb both one and two-dimensional movements, and that the size of the illusion is influenced by the reliability of the afferent feedback coming from the muscle.

1. Inglis et al, 1990 10.1007/BF02423506
2. Bock et al, 2006 10.1016/j.jneumeth.2006.09.010

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Poster

PSTR348: Sensory Processing in Motor Control

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Title: Comparing the effectiveness of synchronous and asynchronous neuromuscular electrical stimulation in controlling human arm movement

Authors: *A. S. KOROL[1], S. YAKOVENKO[2], V. GRITSENKO[3];
[1]Neurosci., West Virginia Univ., Morgantown, WV; [2]Human Performance, West Virginia Univ., Morgantown, WV; [3]Human Performance - Physical Therapy, West Virginia Univ., Morgantown, WV

Abstract: Surface neuromuscular electrical stimulation (ES) is commonly employed to aid in the rehabilitation of motor function and to address limb weakness. Yet, the technique faces limitations that hinder its adoption as a widespread assistive technology. One significant challenge is ES causes the reversed recruitment order of muscle unit activation, leading to rapid muscle fatigue. With graded current or frequency, ES evokes a non-linear “all-or-none” muscle response, which is not suitable for tasks requiring nuanced control, such as precise hand movements. Pain and paresthesia are additional barriers that can discourage the long-term application of ES. Therefore, it is crucial to develop a better ES method that minimizes fatigue, discomfort, and sensory issues while enabling variable muscle control. Typically, ES is applied by passing current through a pair of large electrodes. The muscle force in response to ES is modulated by varying the current amplitude and/or the frequency of electrical pulses. However, a new technique called asynchronous ES (aES) has demonstrated less fatigue in major leg muscles. This method utilizes two or more electrode pairs, allowing current pulses to alternate between them. This alternation asynchronously activates adjacent muscle fibers, which more closely mimics the natural pattern of neuromuscular activation. The objective of our study is to evaluate the impact of aES on fatigue in smaller arm muscles. Additionally, we will explore its effects on paresthesia and the precision of force production, potentially offering a more efficient and less

fatiguing method of muscle stimulation. Ten healthy volunteers performed passive elbow flexion/extension movements evoked by two types of stimulation of their biceps and triceps muscles: ES through one electrode pair and aES through two electrode pairs. We were able to induce consistent force responses and manipulate elbow joint stiffness using the aES protocol. We found that aES produces higher forces at lower current amplitudes than synchronous ES as evidenced by larger movements evoked by aES compared to ES. Lower currents were associated with lower ratings of paresthesia during stimulation. Furthermore, in four participants in whom ES induced complete fatigue, aES caused reduced muscle fatigue during a separate session. Overall, these results are promising for the aES utility as an assistive technology.

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Poster

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Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.04/H33

Topic: E.04. Voluntary Movements

Support: NSERC Grant 2019-04513

Title: The role of afferent vs efferent signals in implicit sensorimotor adaptation

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Abstract: Implicit sensorimotor adaptation has been proposed to be driven by error signals created by discrepancies between various sensory information sources. While proprioception has been proposed as a critical sensory source for the error signal driving adaptation, the role of the sensory prediction derived from the action-related efference copy has largely been neglected. Current task protocols do not typically separate afferent and efferent contributions; thus, their individual roles in implicit adaptation are poorly understood. The purpose of this study was to examine the effect of dissociating the afferent and efferent information available during implicit adaptation. The clamped visual feedback task where participants reach towards targets on a visual display while observing task-irrelevant rotated cursor feedback has been previously used to examine implicit adaptation. Despite awareness of the manipulation and instructions to ignore the visual feedback, participants' reach direction gradually drifts in the opposite direction of the cursor, eventually reaching an upper bound. In the current study, we dissociated afferent and efferent contributions to adaptation through an isometric aiming task. Instead of performing actual reaching movements, participants moved a visual cursor towards radial targets by applying horizontal forces to a fixed handle at a central home location. During perturbation trials, the cursor followed an invariant path rotated relative to the target. Participants were instructed to ignore this task-irrelevant cursor feedback and continue to "reach" towards the target. We found

that participants implicitly adapted in the isometric task, even when the hand never actually moved to the target. Moreover, the level of adaptation observed surpassed that of a typical clamped reaching paradigm by nearly twofold. This finding was confirmed in a secondary experiment where participants performed actual reaching movements and demonstrated significantly less adaptation. Although the isometric task did not remove proprioception itself, it decoupled this feedback from providing target-relevant hand position information. Thus, these findings suggest that while afferent proprioceptive feedback of hand position at the target location most likely plays a role in adaptation behaviour, it is not necessary to induce adaptation. The results of this study highlight the importance of the motor-related efferent prediction towards adaptation behaviour in current computational models of implicit sensorimotor adaptation.

Disclosures: A. Szarka: None. **G. Eschelmuller:** None. **N. Butler:** None. **H.E. Kim:** None. **J. Inglis:** None. **R. Chua:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.05/H34

Topic: E.04. Voluntary Movements

Support: DFG Grant 222641018

Title: Dynamic temporal modulation of somatosensory evoked potentials during reaching

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Abstract: During movements made without visual feedback, tactile perception on a moving finger varies throughout the motion. For example, while it has been shown that perception is worse at the start and end of the movement compared to when at rest, it becomes comparable to rest around the time of maximal velocity (Voudouris & Fiehler, 2021, Sci. Rep., 11). This modulation likely stems from the need for somatosensory feedback for movement control, especially when visual input is absent and participants need to rely on somatosensory feedback only. Although both low and high levels of processing contribute to the suppression of tactile sensations during movement, it is unclear at what stage this dynamic modulation occurs. To investigate this, we recorded somatosensory evoked potentials (SEPs) in the EEG while participants reached for either the left hand's index finger or thumb. Vibrations (20 ms, 280 Hz) were applied to the right index finger at five time points (50, 150, 250, 350, 450 ms post-movement onset). On average, the movements lasted 638 ms and participants reached the maximum velocity 180 ms after movement onset. SEPs following the vibrations reveal P50, P100, N140, P200 and P300 components in centro-parietal electrodes contralateral to the

stimulation. Preliminary results show a significant decrease in the P300 amplitude during movement compared to rest, indicating tactile suppression during reaching. Furthermore, stimulations at 150 and 250 ms, near maximal velocity, show a trend towards a larger P50 amplitude compared to later or earlier ones, though not significantly different. This suggests that in the absence of vision, somatosensory processing is enhanced around the time of maximal movement speed, relative to the start and end of the reach. Meanwhile the amplitudes of the P200 and P300 scale with the latency of the stimulation during movement with the earliest stimulation showing significantly higher amplitudes compared to the latest. Overall these preliminary data suggest a distinct involvement of both early and later stages of cortical processing in the dynamic modulation of tactile perception during movements.

Disclosures: E. Fuehrer: None. **D. Voudouris:** None. **L. Maurer:** None. **K. Fiehler:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

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Program #/Poster #: PSTR348.06/H35

Topic: E.04. Voluntary Movements

Support: NSF BCS 2024923
NSF DGE 1746045

Title: Localizing inverse kinematic representations for motor control in human cortex by simulating embodied agents

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Abstract: To accurately control movements, the central nervous system must solve the "inverse kinematic problem," computing the muscle activations necessary to move the body from an (estimated) current state to a desired position. However, since this inverse mapping is inherently high-dimensional, often lacking a unique, closed-form solution, it is difficult to make concrete predictions about what patterns of neural activity implementing such a computation would look like. Consequently, functional neuroimaging methods have made little progress identifying the neuroanatomical substrate implementing the inverse kinematic model putatively residing within the sensorimotor system. Leveraging recent advances in biomechanical/physical simulation, deep reinforcement learning, motion tracking, and precision neuroimaging, human functional magnetic resonance imaging (fMRI) data from a postural control task can be fit to the internal representations of a deep neural network that has learned to perform the same task in a physics simulation - thus approximating an inverse kinematic model. We show that these inverse kinematic representations of motor states can better predict neural activity in early visual cortex than can the subjects' motion data alone. In a second experiment with the same subjects, we show that cortical areas to which inverse kinematic representations were localized days prior

predicted participants' subjective experience of control (or lack thereof) when we disrupted their neuromuscular kinematics via electrical stimulation of muscles in the forearm. Taken together, our findings indicate that inverse kinematic representations for the control of the hand can, surprisingly, be found in early sensory - not canonically motor - cortical areas, and that these representations are reflected in the conscious experience of directing movement. Moreover, we provide proof-of-concept for a novel neurocomputational approach with which to interrogate the motor system with far more precision than has previously been possible in humans.

Disclosures: J.P. Veillette: None. **P. Lopes:** None. **H.C. Nusbaum:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.07/H36

Topic: E.04. Voluntary Movements

Title: Reinforcement feedback and use dependent processes lead to implicit shifts in perceived sensory states

Authors: *J. H. BUGGELN[1], A. M. ROTH[2], N. MUSCARA[1], J. A. CALALO[2], T. NGO[1], S. SULLIVAN[1], M. CARTER[3], J. CASHABACK[1];
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Abstract: From the satisfaction of striking a golf ball to playing a clean note on an instrument, the motor system desires to hit sensory targets. A powerful idea in sensorimotor neuroscience is that there is not only motor adaptation, but also sensory adaptation. Past work shows that errors lead to sensory recalibration, where there is an implicit shift in the perceived state from the actual state. Yet it is unclear how reinforcement or use-dependent processes may uniquely contribute or interact to influence implicit sensory recalibration. Here we test whether reinforcement or use-dependent processes uniquely contribute or interact to modulate implicit proprioceptive recalibration. Participants moved an arc shaped cursor from a start position to an arc shaped target. The radial position of the arc shaped cursor was aligned with the radial hand position, but was not influenced by the angular hand position. During the reach, the arc shaped cursor increased in size to maintain a constant angular width. The angular redundancy in the cursor and target allowed for movement along the redundant angular dimension, without influencing task success. Participants performed baseline trials, passive trials, and probe trials. During baseline trials, participants were first asked to reach the target center to capture any movement bias. On each passive trial, participants were passively moved by a robot to a consistent location that was away from the target center. During these passive trials, we manipulated both reinforcement feedback and use-dependent processes. We used two groups to manipulate reinforcement (N = 60). One group was told they were moved to a successful location and given positive reinforcement (pleasant noise, target briefly changed colour) on

every passive trial. The other group was told they were unsuccessful on every passive trial. Critically, all participants were moved to the same location and saw the same target. To manipulate use-dependency, we controlled the amount of repetition for both groups. Specifically, we performed probe trials after 15 passive trials (low use-dependence) and 350 passive trials (high use-dependence). During probe trials, participants were asked to reach toward the target center. These probe trials allowed us to test whether a participant had a shift in hand angle relative to baseline, providing a metric of proprioceptive recalibration.Our results showed a main effect of reinforcement ($p = 0.001$) and repetition ($p < 0.001$) on hand angle, but no interaction effect ($p = 0.407$). Collectively, these results support the idea that reinforcement and use-dependent processes independently influence implicit proprioceptive recalibration.

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Poster

PSTR348: Sensory Processing in Motor Control

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NIH/NINDS Grant U01NS123127
Neilsen Postdoctoral Fellowship Research Grant 731621

Title: Probing Touch Perception with Near-threshold Vibrotactile Stimulation during Human Single Neuron Recording

Authors: *B. LIU[1], D. BJANES[1], K. PEJSA[1], B. LEE[2], C. LIU[3], R. A. ANDERSEN[1];
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Abstract: Touch is one of the most fundamental and important senses in humans. Conscious perception in somatosensory processing enables humans to execute dexterous control and interact adeptly with the environment. Somatosensory cortex (S1) and posterior parietal cortex (PPC) have been considered as an integral part in somatosensory processing. However, how S1 and PPC contribute to conscious somatosensation in the human brain is not well understood. To investigate the role of S1 and PPC in somatosensory perception, we conducted a vibrotactile near-threshold study in a clinical trial with two tetraplegic participants. Mechanical vibrotactile stimuli were applied to discrete sensate locations on the hand and arm (inside and outside the somatotopic regions of the S1 arrays). Single neuron data were recorded simultaneously from

chronically implanted Utah arrays in the somatosensory cortex, supramarginal gyrus (SMG) and anterior intraparietal area (AIP). The intensity of the mechanical stimulus was held at a constant near-threshold value, determined with a one-up three-down task to identify the vibrotactile perceptual threshold. We observed PPC neurons encoding two global cognitive variables of the applied mechanical stimuli: the sensory perception (felt versus not-felt) and the confidence rating. An LDA classifier could significantly discriminate between reported felt versus not-felt trials, regardless of what body region was stimulated (inside or outside the somatotopic regions of the S1 arrays). We observed significantly greater tuning to felt versus not-felt trials. Additionally, PPC neurons exhibited higher tuned activity during high versus low confidence rated trials, with the least tuning observed during not-felt trials. In contrast, somatosensory neurons exhibited highly localized tuning, encoding stimulus variables such as stimulus intensity and sensory perception, only if the mechanical stimulus was applied within the somatotopic region covered by the array. These neurons likely do not encode cognitive variables such as confidence, as trials with reported high or low confidence ratings did not show additional tuning compared with trials where the participant did not feel the stimulus. These results provide direct single-neuron evidence for the distinct and critical roles that PPC and somatosensory cortex play in the somatosensory processing. The current study reveals the neural substrates underpinning conscious somatosensation and has significant implications for the restoration of somatosensation through artificial tactile perception.

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Poster

PSTR348: Sensory Processing in Motor Control

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Topic: E.04. Voluntary Movements

Support: NIH Grant UH3NS107714

Title: Proprioception encoded in the motor cortex allows for better decoding generalization to active movement as compared to visually triggered motor imagery

Authors: *S. N. JOHNSON[1], M. RYBAR[2], J. E. DOWNEY[2], N. G. HATSOPOULOS[2]; [1]Committee on Computat. Neurosci., Univ. of Chicago, Chicago, IL; [2]Dept. of Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: The involvement of the motor cortex in controlling both native limb and imagined movements is well-established. However, the extent of overlap between the neural representations and dynamics of motor control in these two contexts is still unclear. This question holds particular significance in the context of brain-computer interfaces (BCIs), which decode neural signals to control output devices like dexterous bionic hands for individuals with

limited motor control. For BCI users lacking motor control, the standard practice involves training a BCI decoder using neural activity while the subjects observe and imagine performing movements presented to them. Therefore, significant differences in neural ensembles between observation-based imagined and native limb movements could have important implications for the BCI community. In this study, we attempt to explore action and motor imagery similarity through a decoding approach. As part of a clinical trial, two subjects with residual movement in the upper-limb following incomplete spinal cord injury were implanted with chronic electrode arrays in the precentral gyrus. Subjects performed center-out reaching movements under three conditions: imagined reaches while observing a virtual arm completing the task ("imagined"), native limb reaches ("action"), and passive movements, where participants imagined reaching while their arm was moved for them ("passive"). Kalman filter decoders were trained on velocity vectors in each of these three conditions and tested across different conditions. While the decoder trained on the imagined condition effectively decoded the velocity of the virtual arm, it could not generalize to decoding native limb movement in either the passive or action conditions. However, the decoder trained on the passive condition more accurately generalized to decoding native limb movement, supporting the conclusion that proprioceptive information allows for better kinematic decoding in BCIs. Consequently, we assert that the difficulty of generalizable decoders reveal important differences in neural representation between native and imagined movements, and propose the use of passive movements as a way to address these differences. These results prompt careful consideration in the application of BCI technologies.

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Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.10/H39

Topic: E.04. Voluntary Movements

Support: PJT-159 559

Title: Caudal motor cortex has a greater change in activity during rapid corrections to proprioceptive and visual perturbations than rostral motor cortex and premotor dorsal cortex

Authors: *M. T. JACOBS[1], K. P. CROSS[2], A. KUMAR[3], S. H. SCOTT[4];
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Abstract: A key feature of the motor system is the ability to rapidly generate goal-directed motor corrections to counteract disturbances of the limb. Recently, our lab demonstrated that responses generated from rapid corrections to visual and proprioceptive perturbations recruit significantly overlapping neural populations in rostral M1[1]. The present study explored if this result was regionally specific across motor cortex. In particular, PMd receives anatomical projections from visually dominant parietal areas, whereas caudal M1 preferentially receives anatomical projections from proprioceptively dominant parietal areas. Consequently, we predicted a gradient in neural responses to sensory feedback with greater responses to visual versus proprioceptive responses in PMd, the reverse to be observed in caudal M1, and rostral M1 displaying equal responses, as we have previously observed. A male macaque was trained to perform reaching movements using the Kinarm robotic lab. A cursor (circle) represented finger position in a virtual reality system aligned with the horizontal workspace. On random trials, either the cursor was shifted (visual perturbation) or a mechanical load was applied to the limb (proprioceptive perturbation) requiring the monkey to make a motor correction to attain the spatial goal. Perturbations occurred perpendicular to the lateral reach movement (i.e., away, or toward). A chamber was implanted to allow individual micro-electrodes to be inserted transdurally permitting neural recordings across arm-related motor cortex. Recordings were located in caudal bank of M1 (n = 32), rostral M1 (n = 28), and PMd (n = 38). Unexpectedly, there were no significant differences mediated by perturbation type across the 3 motor areas. The change in activity in caudal bank of M1 was significantly larger than both other regions regardless of perturbation type (Kolmogorov-Smirnov, Bonferroni correction = 3, all conditions $p < 0.016$) (mean Δ activity, proprioceptive: caudal M1 = 19.09 ±9.62, rostral M1 = 15.09 ±8.72, PMd = 12.99±8.05 spikes/sec, visual: caudal M1 = 14.28 ±8.77, rostral M1 = 11.73 ±6.15, PMd = 12.99 ±8.05 spikes/sec). These results imply sensory integration has occurred either at the level of motor cortices or upstream, potentially in parietal cortical regions. 1. Cross, K. P., Cook, D. J., & Scott, S. H. (2024). *eNeuro*.

Disclosures: M.T. Jacobs: None. **K.P. Cross:** None. **A. Kumar:** None. **S.H. Scott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stephen H. Scott is the co-founder and Chief Science Officer of Kinarm, which commercializes the robotic technology used in the present study..

Poster

PSTR348: Sensory Processing in Motor Control

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Topic: E.04. Voluntary Movements

Support: NIH R01 Grant NS112367
NSF Grant 2319108

Title: Generalization of visual and proprioceptive changes after visuo-proprioceptive recalibration

Authors: *M. WALI[1], R. MATHARU[2], C. LO[2], R. ELIE[2], R. WATTERSON[2], G. HALE[2], J. MATTEN[2], B. S. ISA[2], H. J. BLOCK[3];
[1]Dept. of Kinesiology, Indiana Univ. Bloomington, Bloomington, IN; [2]Indiana Univ., Bloomington, IN; [3]Dept. of Kinesiology, Indiana Univ., Bloomington, IN

Abstract: Multisensory integration of visual and proprioceptive cues about hand position gives us flexibility to cope with internal and environmental changes. If visual and proprioceptive cues become spatially mismatched, the brain compensates by shifting the proprioceptive estimate closer to the visual estimate (proprioceptive recalibration) and vice versa (visual recalibration). Some evidence suggests the proprioceptive recalibration that accompanies visuomotor adaptation generalizes broadly, but the principles governing generalization of recalibration in response to a cue conflict are unclear. In Experiment 1 we asked whether visual and proprioceptive recalibration generalize across different workspaces. In Experiment 2 we asked whether visual recalibration generalizes across visual cues that have a different color, shape, size, or position. Participants completed several blocks of trials in a 2D-VR touchscreen apparatus. They were asked to estimate the location of visual (V), proprioceptive (P), and combined (VP) targets associated with their left index finger using their unseen right finger to point. No performance feedback or knowledge of results was given at any time. In Experiment 1, three groups experienced a misalignment block in which the V target gradually shifted 70 mm forward from the P target in a central workspace (body midline) or 10 cm to the left or right of the body midline. Before and after the mismatch block, participants performed V, P, and VP trials in all three of the workspaces, in random order. Preliminary data (N=21) suggests that both visual and proprioceptive recalibration generalizes across workspaces. On average, proprioception recalibrated 14.0±12.1 mm (mean ± 95% CI) in the trained workspace and 10.6±7.3 mm in the untrained workspaces. Visual recalibration in the trained and untrained workspaces was 26.4±17.0 and 35.0±15.2 mm, respectively. Experiment 2 groups performed all trials in the central workspace, with the mismatch block flanked by a pre-and post-mismatch block consisting of a small number of V, P, and VP trials, and a larger number of "alternative" V trials (altV). Depending on group assignment, the altV trials could differ from V trials (white square) in color (cyan or magenta), shape (diamond or circle), size (36 mm instead of 12 mm), or placement (random locations in the workspace or consistent offset from the normal position). In preliminary data (N=15 total), visual recalibration shows evidence of generalization to visual cues with different appearances and positions. Our findings so far are consistent with broad generalization of recalibration in response to a visuo-proprioceptive cue conflict.

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Poster

PSTR348: Sensory Processing in Motor Control

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Program #/Poster #: PSTR348.12/I1

Topic: E.04. Voluntary Movements

Support: NIH NINDS NS116883

Title: Explicit sensorimotor strategies fail to launch in response to small perturbations

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Abstract: Sensorimotor adaptation tasks engage multiple learning processes in response to an experimentally imposed perturbation. The mismatch between predicted and expected sensory feedback engages an implicit process that serves to recalibrate the sensorimotor map. If the perturbation is large, the participant may strategically re-aim to counteract the perturbation. In this study, we examine strategy use in response to small, incremental perturbations and how this process is modulated by implicit recalibration.
Using a web-based platform, participants (n=50/group) were tested on a visuomotor rotation task in which the size of the rotation was incremented in small steps of 1.5° to reach an asymptotic value of 60°. One group received endpoint feedback immediately after reaching, engaging both implicit and explicit processes. The second group received endpoint feedback after an 800 ms delay, a manipulation that abolishes implicit adaptation, requiring explicit strategy use to counteract the perturbation. Turning to the strategy use question, we looked at performance changes early and late in response to the perturbation. During the early phase (perturbation size: 1.5 - 15°), change in hand angle was reduced in the Delay group (1.0°) compared to the No-Delay group (4.8°). The negligible change in hand angle for the Delay group suggests explicit strategy use 'fails to launch' in response to an incremental perturbation, even when the perturbation size reached 27°. When the perturbation reached 60°, the change in hand angle for the Delay group nearly compensated for the error (55.0°). Thus, when the perturbation became sufficiently large, participants in the Delay group had successfully identified a re-aiming strategy.
Interestingly, the No-Delay group showed a much smaller change in hand angle (34.2°) at this phase of the experiment. As part of its operation, implicit recalibration may suppress strategy use. Alternatively, performance changes arising from implicit recalibration may be sufficient to preclude the launching of an aiming strategy. To evaluate these hypotheses, we focused on the data from individuals who demonstrated strategy engagement (Delay(n): 22, No-Delay: 29). There were no significant differences between Delay and No-Delay groups when the perturbation size reached 60°, even though a substantial part of learning for the No-Delay group was implicit (evident by their aftereffect of 19.2°). These results argue against the suppression hypothesis; rather, it appears that for a subset of participants in the No-Delay group, changes in performance from implicit recalibration were sufficient to preclude the deployment of a re-aiming strategy.

Disclosures: E. Cisneros: None. **R. Ivry:** Other; co-founder with equity in Magnetic Tides, Inc.. **J.S. Tsay:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

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Program #/Poster #: PSTR348.13/I2

Topic: E.04. Voluntary Movements

Title: Long-latency feedback responses in the lower limb are modulated by smooth pursuit eye movements (SPEM) during mechanical perturbations

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Abstract: Achieving success in daily activities hinges on effectively responding to unforeseen mechanical disruptions affecting our limbs and body. Central to this capability is the long-latency reflexes (LLR), which is a feedback response evoked by an unexpected perturbation and is mediated by transcortical pathways. Despite its significance, the influence of eye movements on adjusting this LLR gain is yet to be understood. In our previous studies, we demonstrated that smooth pursuit eye movements (SPEMs) play a crucial role in modulating anticipatory postural adjustments (APAs) before contact with a moving object. Specifically, we found that constraining SPEM diminishes APAs. Building on this finding, we hypothesized that constraining SPEM would also alter LLRs during unexpected mechanical perturbations in the upper and lower extremity muscles. Nine right-hand dominant healthy adults (age: 22.6 ± 0.8 years, 5 females) with no known neurological disorders grasped a Kinarm robotic manipulandum with their right hand and were instructed to stabilize their virtual hand inside a virtual rectangle (1×1 cm) while standing on a force plate The objects moved at the same speed (25 cm/sec) towards the participants under various gaze conditions, including central fixation (32 trials, 10 blocks), and SPEMs (32 trials, 10 blocks) randomized between participants. In 20% of the trials, a mechanical perturbation (10N towards or away from the body) was randomly applied. We measured eye movements, limb kinematics, and muscle activity in three right upper limb muscles (triceps brachii, posterior deltoid, and pectoralis major) and one lower limb muscle (tibialis anterior) on the left and right legs. We quantified the amplitude for each muscle in three different time windows from the mechanical perturbation: R1 (25 to 45 ms), R2 (45 to 75 ms), and R3 (75 to 100 ms for the upper limb; 75 to 120 ms for lower limb). We conducted a repeated measures ANOVA to quantify the effects of gaze on the mean EMG amplitude at the outlined time windows. We found no main effect of gaze in any of the upper limb muscles across any of the time windows. However, we observed a significant effect of gaze in the tibialis anterior muscles (right [$F(1,23) = 4.7$, $P < 0.001$, $\eta^2 = 0.12$] and left [$F(1,23) = 5.2$, $P < 0.05$, $\eta^2 = 0.02$]). The fact that SPEMs affect LLRs in lower limb muscles but not in upper extremity muscles suggests that the cerebellum and brainstem likely regulate both SPEM and upright posture stabilization through shared control mechanisms.

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Poster

PSTR348: Sensory Processing in Motor Control

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Topic: E.04. Voluntary Movements

Support: NIH Grant R21NS121624

Title: Rapid tuning of mid-movement error corrections in response to visual and haptic perturbations during manual interception of moving targets

Authors: *R. A. SCHEIDT[1], P. GONZALEZ POLANCO[1], D. VANDER HEIDEN[1], A. GRADY[1], K. D. BASSINDALE[1], C. OTTEMAN[3], L. A. MROTEK[1,2], S. A. BEARDSLEY[1], K. A. NIELSON[3], E. R. PAITEL[3];
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Abstract: The ability to modify ongoing actions to correct errors that arise during performance is critical for survival. Previous studies show that the latency and accuracy of error corrections depend on how much time it takes to process relevant sensory information to form motor command updates. Here we show that preparatory state also influences error correction latency. We performed two sets of experiments wherein participants grasped the handle of a planar robot that imposed a nominal viscous resistance to hand movement. Participants watched a target move pseudo-randomly just above the horizontal plane of hand motion and then initiated quick interception hand movements when given a GO cue. In one set of experiments, GO cues occurred without warning with a random delay relative to target motion onset. In the other experiment, participants were given audio pre-cues such that GO cue timing was predictable. On some trials, the robot's viscosity or the target's speed changed without warning when the hand started to move. We fit a sum-of-Gaussians model to mechanical power measured at the handle to determine the number, magnitude, and relative timing of submovements occurring in each interception attempt. Reaction times relative to the GO cue reflected the pre-cue conditions (pre-cue: 74±108ms; no pre-cue: 399±73ms). Capture times also reflected the pre-cue conditions for trials where a single submovement successfully intercepted the target; capture times averaged 410±89ms with pre-cues and 264±73ms without pre-cues. Sometimes, two or more submovements were required. Error correction latencies were considerably shorter when the initial movement was pre-cued (217±38ms) than when the GO cue occurred unpredictably (477±120ms). With pre-cues, the initial error corrections occurred on average ~200ms *before* feedback could have indicated that the target had been captured or missed. Without pre-cues, error correction latencies occurred ~200ms *after* the expected time of target capture. In both experiments, initial error corrections were well-tuned to the altered testing conditions; speed/viscosity decreases elicited less vigorous corrections than in control trials with unprovoked errors; speed/viscosity increases elicited more vigorous corrections. These results demonstrate that the brain monitors and predicts the outcome of evolving movements, rapidly infers causes of mid-movement errors, and tunes movement plans for corrective action accordingly. This all happens very quickly, within ~217ms of initial movement onset when that onset can be

anticipated (when pre-cued). By contrast, trials that start in a reactive manner appear to also conclude reactively.

Disclosures: R.A. Scheidt: None. **P. Gonzalez Polanco:** None. **D. Vander Heiden:** None. **A. Grady:** None. **K.D. Bassindale:** None. **C. Otteman:** None. **L.A. Mrotek:** None. **S.A. Beardsley:** None. **K.A. Nielson:** None. **E.R. Paitel:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.15/I4

Topic: E.04. Voluntary Movements

Support: NSERC grant - Discover Grant: 2017 - 04829

Title: Rapid feedback responses during transitions between posture and movement when planning, performing, and terminating goal-directed reaching movements.

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Abstract: Humans can perform actions with different goals like holding the arm in a fixed posture or performing a movement. Consider the example of holding a glass of water versus reaching to place it on a table. This simple action requires disengaging from posture to perform and terminate a movement. In healthy people, these transitions occur seamlessly, although past studies suggest the neural control may differ between posture and movement. We know little about the control mechanisms that support the transition between these distinct goals. Here, we examined corrective responses to mechanical disturbances to gain insight into how the neural control of sensory feedback differs when healthy participants disengage from posture to perform and terminate reaching movements. Participants (n = 20) performed planar reaching movements while seated with their dominant arm supported by the adjustable linkages of a robotic exoskeleton (Kinarm). They moved a hand-aligned feedback cursor into a start position and waited for a visual go cue before reaching to a goal target (12 cm distance). Participants were instructed to complete their movements within 200-400 ms of leaving the start position and received explicit feedback about the timing of their movements. Mechanical perturbations (±2 Nm) were randomly applied on 50% of trials, interleaved with unperturbed trials, to displace the elbow into flexion or extension. The perturbations were applied 750, 250, and 0 ms before the go cue while participants maintained posture, during reaching at 0, 25, 50, 75, and 100% of the reach distance, or 250 and 750 ms after terminating the reach and reengaging posture in the goal target. We quantified the vigor of corrective responses using the peak lateral displacement of the participant's hand. We recorded the activity of elbow muscles to assess responses to stretch or shortening. We found that participant's muscle responses were larger and their arm was

displaced less during movement compared to when they held posture prior to movement or after reengaging posture in the goal target. Additionally, muscle responses were larger and peak displacements were smaller when reengaging posture in the goal target compared to maintaining posture before movement. The observed changes in behaviour were linked to flexible and distributed responses of the stretched agonist and shortened antagonist muscles. Overall, our findings demonstrate that the nervous system alters its neural control when transitioning from posture to movement (and vice versa), such that it is more sensitive to sensory feedback when moving and least sensitive when maintaining posture before movement.

Disclosures: J. Rancier: None. **P. Maurus:** None. **T. Cluff:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.16/I5

Topic: E.04. Voluntary Movements

Support: Penn State Start-Up Funds

Title: Age-related changes in motion processing impact predictive posture stabilization during mechanical interactions with moving objects

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Abstract: Postural stabilization relies on anticipatory postural adjustments (APAs), which are feedforward mechanisms to maintain stability and are known to deteriorate with age. When interacting with moving objects, individuals adjust their posture against the forces experienced during a collision, tailoring these adjustments according to the speed of the object. This adaptation involves processing motion through retinal signals and smooth pursuit eye movements (SPEM), which help in accurately predicting object motion for effective posture stabilization. This study explores how older adults track object motion actively through SPEM and passively through retinal processing within different sections of the visual field for modulation of APAs. Right-hand dominant healthy older adults (mean age: 72.4) and young adults (mean age: 21.3) grasped a Kinarm manipulandum with their right hand and were instructed to stop virtual objects by matching the force felt on collision. The objects moved at 4 speeds (15, 21, 27, and 33 cm/sec) toward the participant under 3 gaze conditions: central fixation (FC), peripheral fixation (FLR), and SPEM. We hypothesized that impaired motion processing in older adults' peripheral vision would affect the timing and magnitude of their APAs. We measured eye movements, limb kinematics, and kinetics. We observed that participants increased their hand force and moved slightly towards the object before contact, typically reaching maximum force before contact, termed peak anticipatory force (AFpeak). We

also calculated the time at which the hand force increased above baseline levels as an index of timing (TCFon). A three-way ANOVA tested the effects of age, gaze condition, and object speed on these measures. We observed significant age-related differences in TCFon and AFPeak. Older adults increased force above baseline levels earlier than young adults and generated higher AFPeak than the younger adults ($P < 0.001$). Interestingly, in younger adults, APAs were not significantly different between gaze conditions FLR and SPEM. However, in older adults, APAs were significantly different between FLR and SPEM ($P<0.05$), indicating degraded motion processing in the visual periphery. The results suggest that age-induced decrements in motion processing impact the timing and amplitude of APAs. Interventions aimed at improving motion processing in the visual periphery may benefit older adults in preparing postural adjustments that lead to stable interactions during motion-based actions.

Disclosures: O. Sinha: None. **T. Rosenquist:** None. **T. Singh:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.17/I6

Topic: E.04. Voluntary Movements

Support: RGPIN-2024-0446
RGPIN-2018-06068
Queen's Internal Award

Title: Muscular co-contraction improves rapid upper limb corrective responses to mechanical perturbations during postural control

Authors: *D. ARMSTRONG[1], S. H. SCOTT[2];
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Abstract: Muscular co-contraction emerges in unstable environments and when learning unstable dynamics, but does it improve performance? We tested whether muscular co-contraction (simultaneous activation of agonist and antagonist muscle groups) improved performance in a postural perturbation task. Ten participants (4 ♀, 6 ♂; stature = 1.74 ± 0.10 m; body mass = 76.4 ± 11.7 kg; age = 25.7 ± 3.2 yrs) completed the study protocol. A Kinarm Exoskeleton Robot was used to apply a transient 5 Nm torque (10 ms ramp, 50 ms duration) to the elbow joint after the participant held their fingertip at a spatial target for a random time between 2-4 seconds. Shoulder position was held static using the Kinarm robot. In the first pre-perturbation activity condition either the stretched or shortened muscle groups resisted 5 Nm background loads before the transient load was applied. For the co-contracting condition, 2.5 Nm of activation was generated in both the stretched and shortened muscle groups using real-time visual feedback of EMG. In the relaxed condition no pre-perturbation muscle activity was

generated. Ten trials were completed for each pre-perturbation condition, including both transient flexor or extensor torque conditions. Trials were successful when the target was reacquired within 500 ms and held for a subsequent 1000 ms. Maximum elbow displacement and target overshoot were also recorded. Success rates were significantly higher when co-contracting (67.8 ± 7.9%) compared to when one muscle group was pre-loaded (36.7 ± 6.3%) and relaxed (13.0 ± 4.4%). We found perturbations that shortened the pre-loaded muscle group (49.5 ± 23.9%) were more successful than perturbations that stretched the pre-loaded muscle group (22.0 ± 25.8%), with the former approaching performance observed when co-contracting. Critically, these performance differences are attributable to significantly reduced target overshoot in the co-contracting (2.8 ± 0.5^{o}) and shortened muscle pre-load (3.1 ± 1.6^{o}) conditions compared to when the stretched muscle group was pre-loaded (12.8 ± 5.6^{o}) and the relaxed condition (5.6 ± 0.7^{o}). Meanwhile, maximum displacement didn't significantly differ between co-contracting (17.8 ± 1.5^{o}) and pre-loading either the stretched (14.5 ± 4.6^{o}) or shortened (14.0 ± 3.4^{o}) muscle groups, but was significantly lower than the relaxed condition (33.0 ± 2.5^{o}). Consistent findings were observed when replicating the protocol at half the magnitude of pre-perturbation co-contraction and background load levels, albeit with smaller effect sizes. This highlights that muscular co-contraction improves corrective response performance in a postural perturbation task.

Disclosures: D. Armstrong: None. **S.H. Scott:** Other; Co-founder and CSO of Kinarm.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.18/I7

Topic: E.04. Voluntary Movements

Support: NIH Grant R01EB032328

Title: Effects of Increasing Age on Tactile Spatial Pattern Recognition and Hand Function in Older Adults

Authors: G. G. KABIL[1], M. K. WEBER[2], R. N. LOGUE COOK[1], D. DUQUE URREGO[3], C. HAIRE[4], S. M. CAIN[3], A. P. SAMPLE[4], D. T. BURKE[5], P. NEWMAN-CASEY[6], *S. H. BROWN[1];
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Abstract: Age-related declines in tactile sensibility have primarily been examined using clinical measures of tactile registration - the perception of a stimulus applied to the skin surface. In contrast, little is known regarding the effects of aging on the ability to accurately perceive more

complex tactile spatial patterns, essential for the detection of object characteristics. Based on our previous work demonstrating significant declines in spatial pattern acuity in older adults with little change in tactile registration (Logue et al., 2022), this study examined the effects of increasing age on the magnitude of decline across hand tactile acuity, strength, and dexterity in older adults.
Hand sensorimotor function was assessed in healthy, right-handed young (23-35 yo, n=25), young-older (65-76 yo, n=25), and older-older (76-87 yo, n=24) participants. Standardized clinical assessments included grip and pinch strength, dexterity (Grooved Pegboard Test, Arthritis Hand Function Test - AHFT) and tactile registration (Semmes-Weinstein Monofilament Test). Tactile spatial pattern acuity was measured using a custom-designed device with various raised dot patterns that required participants to select the perceived pattern from several options displayed on a computer screen.
Both older groups performed significantly worse than young adults on all measures ($p<0.02$), with the exception of the AHFT - a timed test involving daily bimanual activities - for which only the 76-87 yo group differed from young adults. When comparing the two older age groups, performance on all tests except for pinch and grip strength was significantly worse in the 76-87 yo group ($p<0.05$). However, the magnitude of decline varied across tasks, with the smallest decline observed for grip strength (9.3%) and the largest declines in tactile spatial pattern acuity (accuracy: 20.2%, time to select perceived pattern: 24.5%). In contrast, tactile registration scores did not change between the two older groups.
These results indicate that, with increasing age in healthy older adults, the magnitude of decline across measures of hand strength, tactile acuity, and dexterity is not uniform. Greater declines in tactile spatial pattern recognition may be due to age-related changes in peripheral neural pathways associated with tactile perception, as well as subtle higher-order cognitive declines associated with central processing of afferent feedback. Lastly, given the importance of daily hand manipulation skills affecting, for example, medication adherence such as eye drop instillation, there is a critical need for the development of more sensitive yet easy to use hand assessment tools for clinical use.

Disclosures: G.G. Kabil: None. **M.K. Weber:** None. **R.N. Logue Cook:** None. **D. Duque Urrego:** None. **C. Haire:** None. **S.M. Cain:** None. **A.P. Sample:** None. **D.T. Burke:** None. **P. Newman-Casey:** None. **S.H. Brown:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.19/I8

Topic: E.04. Voluntary Movements

Support: NIH-R37-HD087089
NIH-R01-CRCNS-NS120579
NSF-M3X-1825942

Title: Interacting with Complex Objects sans Haptic Information: Predictability and Stability

Authors: *S. BAZZI[1], M. SADEGHI[2], R. SHARIF RAZAVIAN[3], D. STERNAD[4];
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Abstract: Humans have a remarkable ability to sense and process information about the world they interact with. This is of particular importance when we physically interact with objects, where haptic feedback provides a continuous stream of information about object properties. For objects with internal dynamics, such as a cup filled with coffee, where the user has only indirect control over these dynamics, haptic information may play a crucial role. Previous work on transporting a simplified "cup of coffee" has shown that humans seek predictable and stable interactions. When denied haptic information regarding internal dynamics of the system, can subjects still purposefully handle the object? To examine these questions, 3 experimental conditions were designed that manipulated haptic information in a virtual environment where subjects interacted with a cup-and-ball system. In each condition (120 trials), 9 subjects were instructed to move the system rhythmically for 15s paced by a metronome at 0.6Hz. In the first condition, subjects received full visual and haptic information about the object dynamics (*Fully Coupled*). In the second condition, the ball mass was reduced to a value close to zero (*Massless Ball*). While seeing the movements of the ball, there were no ball forces acting on the hand, except the inertial forces from moving the cup. The third condition eliminated all haptic feedback from both the cup and the ball, such that the visible ball acted solely on the visible cup on the screen; no inertial or ball forces were felt by the user (*Decoupled*). By progressively reducing the haptic feedback, we tested how predictability and stability were affected. In addition, at the start of each trial, subjects could interact with the cup-and-ball to explore and prepare its dynamics, potentially learning the system without haptic information. Results showed that subjects increased predictability over trials in all conditions. However, in the *Decoupled* condition subjects moved significantly slower than the pace of the metronome, which neutralized the internal dynamics and helped maintain control of the object. In contrast, stability was compromised in the two conditions where subjects were denied haptic feedback. This indicated that predictability, more than stability, was of paramount importance. Further analysis of the preparatory movements suggested that even when given the chance to explore and prepare the system dynamics, subjects could not learn the object's dynamics without haptic information. These results suggest that haptic feedback plays a critical role in physical interactions with complex objects.

Disclosures: S. Bazzi: None. **M. Sadeghi:** None. **R. Sharif Razavian:** None. **D. Sternad:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.20/I9

Topic: E.04. Voluntary Movements

Support: NIH-R37-HD087089
NIH-R01-CRCNS-NS120579
AJC Merit Research Scholarship (Northeastern University)

Title: Ringing a Bell: Human Control Strategies for Contact-Rich Manipulation of Complex Objects

Authors: *S. ANNAPRAGADA[1], S. BAZZI[3], R. RAZAVIAN[1], D. STERNAD[2];
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Abstract: Humans interact daily with complex objects, such as carrying a bag of groceries or a cup of coffee. Understanding the control of these interactions is critical to advance our understanding of human motor control of natural behaviors. Our previous work on a task emulating the transport of a cup of coffee showed that humans increase predictability and stability of the complex object dynamics. However, the question of how humans manage contact-rich interactions remains unexplored; while seemingly easy for humans, the problem is highlighted in robot control. For example, ringing a bell results in intermittent contacts between clapper and bell, which poses a difficult control problem due to the nonlinear and discontinuous internal dynamics resulting from contact. To address this question, human subjects were asked to ring a virtual bell, consisting of a clapper hanging inside a bell, with the bell's movements confined to a horizontal line. To interact with the bell-and-clapper system, humans used a robotic manipulandum that provided haptic feedback of the contact dynamics. Subjects were asked to ring the bell either at a consistent frequency of their choice or at a fixed frequency, signaled by a metronome. They were free to pick their movement amplitude in both conditions. Subjects repeated 60x20s trials in each of 3 sessions completed over 3 days. Their kinematic and kinetic data were analyzed to convergence toward a preferred pattern. Four control objectives were hypothesized: 1) subjects reduce effort by minimizing contact force; 2) subjects reduce effort by minimizing energy expenditure; 3) subjects maximize stability to reduce the impact of sensorimotor noise; or 4) subjects maximize the predictability of the system.To test these hypotheses, inverse-dynamics simulations of the bell-clapper system were generated. Simulating over viable combinations of bell amplitudes and clapper frequencies, contact force, energy, stability, and predictability were computed, leading to solution spaces that summarized the varying effectiveness for each control objective. Overlaying subjects' chosen amplitude/frequency pairs onto these spaces allowed for an analysis of which control objectives were prioritized. Preliminary analyses indicated that subjects preferred small amplitude movements, which minimized contact forces while satisfying stability and predictability. Although prior work showed that humans prioritized predictability in their interactions with complex objects, this work provided evidence that in contact-rich tasks, the control objective tended towards minimization of contact forces, possibly to improve the controllability of the system.

Disclosures: S. Annapragada: None. **S. Bazzi:** None. **R. Razavian:** None. **D. Sternad:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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Topic: E.04. Voluntary Movements

Support: NIH-R37-HD087089
NIH-R01-CRCNS-NS120579
NSF-M3X-1825942

Title: Exploiting interactive dynamics in the transport of complex objects

Authors: *K. DESABHOTLA[1], R. LOKESH[2], D. STERNAD[3];
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Abstract: A waiter serving a cup of coffee in a café may need to swerve around tables to avoid collisions. In doing so, the waiter exerts forces onto the cup and, indirectly, onto the coffee, that in turn act back on the cup and hand. How do we deal with such internal dynamics generated by our own actions? The forces of the coffee's sloshing can interfere with intended movement risking spilling the coffee. However, these same forces may also assist the movement. This study asked whether interaction forces generated in complex object interactions perturb, or may be actually exploited. Our previous work examined transporting a cup with a rolling ball inside, a cart-and-pendulum system, that has two essential challenges: underactuation and nonlinearity. Several studies found that humans increase the stability and predictability of these potentially unpredictable dynamics. This paradigm was confined to transport on a horizontal line. The present extends the challenge to movements on a horizontal plane with a 3D cup-and-ball system, with the cart displayed as a semi-spherical cup, and the spherical pendulum bob displayed as a ball rolling inside. Subjects (N=15) interacted with the system in a virtual environment where they moved the cup-and-ball and received haptic feedback via a robotic manipulandum. They moved the cup from a "home" to a target position and back, swerving through a via point lateral to the target direction to introduce forces orthogonal to the movement direction. The via points were located above and below the home-target line. Participants were instructed to move as fast as possible without losing the ball. Performance was quantified by duration and length of the curvilinear cup trajectory. The risk of losing the ball was quantified by an energy margin between the ball's current state and its 'escape'. To assess whether participants exploited internal dynamics, the directional alignment between cup dynamics and ball force on the cup was quantified. Results showed that individuals reduced movement time and engaged with riskier ball dynamics. Furthermore, the trajectory segments with aligned ball force and cup dynamics increased with practice, as did the degree of alignment. This strategy tuned the underactuated ball dynamics to align spatiotemporally with the cup dynamics not only to avoid disruption, but to also utilize additional forces generated by the ball. These results present first steps to shed more light on how humans manage the passive dynamics generated by the plethora

of objects that we interact with in daily activities, ranging from bottles of water to putting on a coat. Insights of this work are extended to assessing impairments in populations after stroke.

Disclosures: K. Desabhotla: None. **R. Lokesh:** None. **D. Sternad:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.22/I11

Topic: E.04. Voluntary Movements

Title: Impact of sensory feedback on motor performance in augmented reality

Authors: *S. BONNET[1,2], I. ZHURAKOVSKAIA[2], H. DAUMAS[2], R. ACKERLEY[1]; [1]Ctr. de Recherche en Psychologie et Neurosciences, CNRS Aix-Marseille Univ., Marseille, France; [2]V.RTU, Marseille, France

Abstract: Tasks performed in augmented reality (AR) often have diminished motor performance, due to reduced tactile and proprioceptive inputs. We investigated whether vibrotactile haptic feedback can enhance motor performance within AR environments. Participants performed the Box and Block Task, which challenges individuals to move as many cubes as possible from one side to the other within one minute. The study was approved by an ethics committee and conformed to the Declaration of Helsinki, including obtaining informed consent. Both hands were tested, always starting with the dominant hand. After a familiarization phase, participants undertook five randomized task blocks: performing in real conditions, in AR, and in AR supplemented with either vibratory feedback from a wristband, ring, or bBoth. Quantitative analyses focused on task performance, hit/miss rates, and participant perceptions. Results from 10 participants indicate a significant performance decrease in AR compared to real conditions, with a reduction of 28%. This decrease was less than the 30-40% typically reported in existing literature, suggesting potential moderating effects of the experimental setup. Within the AR conditions, performance was detrimentally impacted by the ring feedback and the combination of both feedback types, while the wristband alone did not yield significant differences. No differences were found between dominant and non-dominant hands. Qualitatively, participants reported a preference for the wristband, which was perceived as more pleasant and effective, that it made the task easier and the participants more efficient. Overall, participants appreciated the haptic feedback, noting it positively impacted their concentration and engagement with the task. Feedback was perceived as consistent and convincing, aligning well with other senses. In conclusion, while AR provides near-realistic visual and auditory inputs, the absence of adequate tactile and proprioceptive input renders tasks far less efficient. Our findings indicate that providing vibration feedback at different locations on the hand does not universally enhance performance. As such, we are exploring other locations and types of vibration to improve motor tasks within AR. This research highlights the challenges of integrating sensory

enhancements in virtual training environments, advocating for a nuanced approach to developing haptic feedback systems that can more effectively complement AR technologies.

Disclosures: S. Bonnet: A. Employment/Salary (full or part-time):; V.RTU. **I. Zhurakovskaia:** A. Employment/Salary (full or part-time):; V.RTU. **H. Daumas:** A. Employment/Salary (full or part-time):; V.RTU. **R. Ackerley:** None.

Poster

PSTR348: Sensory Processing in Motor Control

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR348.23/I12

Topic: E.04. Voluntary Movements

Support: NIH R01 HD088417

Title: Altered movement coordination during functional reach tasks in patients with chronic low back pain and the relation to numerical pain rating scores.

Authors: *S. M. VAN DER VEEN[1], J. S. THOMAS[2];
[1]Physical Therapy, East Carolina Univ., Greenville, NC; [2]Virginia Commonwealth Univ., Richmond, VA

Abstract: Identifying pain levels and movement strategies in chronic low back pain (CLBP) patients has important clinical implications for treatment and reducing the risk of recurrence. While prior research has indicated biomechanics of are altered in CLBP patients. More specifically, CLBP patients show decreased lumbar-hip ratio during forward reach movement, indicating a decrease in contribution of lumbar flexion relative to hip flexion during forward bending. In this study, we aim to explore the relationship of pain and fear of movement within a CLBP population to forward bending patterns. Participants with CLBP (N=145, Male= 53, Age= 39.06±12.95) completed a virtual reality standardized reaching task. This standardized reaching task targets were four individualized positions based on hip height, truck height, and arm length to elicit 15°, 30°, 45°, and 60° lumbar flexion when only the lumbar back would bend with 90° flexion in the shoulder. Whole-body kinematics were collected using a three-dimensional motion capture system, from this data lumbar and hip flexion was used to calculate lumbar-hip ratio (LHratio). Numerical pain rating scale (NRS now, last 24h, week), kinesiophobia (TSK), pain catastrophizing scale (PCS), perceived recovery status (PRS), and the profile of mood (POMS) were taken to identify levels of pain and fear of movement. Seperate regression analysis were caried out (four in total, one for each height) with LHratio as the dependent, and 5 blocks (NRS scores, TSK sub-scores, PCS sub-score, PRS sub-scores, and POMS scores) were completed. Results psychological measures and LHratio for the first (15°) movement height (PCS magnification p=.012, PCS helpless p=.014, and PRS cognitive p=.012). For the second movement height (30°) showed statistically significant relationships for pain measures (NRS Now p=.024 and NRS 24h p=.011) and psychological measures (TSK somatic focus p=.034,

PRS behavior p=.013, and PRS cognitive p=.005). The third movement height (45°) showed statistically significant relationships for pain measures (NRS Now p=.020 and NRS 24h p=.011) and psychological measures (POMP vigor p=.009, and POMS confidence p=.005). The fourth movement height (60°) showed statistically significant relationships for pain measures (NRS Now p=.008 and NRS 24h p=.013) and psychological measure (POMS confidence p=.030). These results indicate the pain right now and over the last 24h are most consistently related to movement strategy. However some of the psychological measures so relationships to LHratio, none of them are consistent for mor that 3 reaching heights.

Disclosures: S.M. Van Der Veen: None. **J.S. Thomas:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.01/

Topic: E.06. Posture and Gait

Support: ASAP-020551

Title: Progressive changes in the behavior of prodromal and parkinsonian iMCI-Park mice

Authors: *A. PAMUKCU[1], K. BODKIN[2], A. KENNEDY[1], D. SURMEIER[3];
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Abstract: Parkinson's Disease (PD) is a slow and progressive neurological disorder that disrupts the brain circuits controlling movement, cognition, sleep, and other aspects of daily living. Although the pathology associated with symptomatic PD is well understood, we do not have a firm grasp of the changes that occur during the prodromal period, before the onset of clinical symptoms of PD. Improving our understanding on this critical stage could lead to earlier diagnosis and interventions that could change the course of the disease.
The Surmeier lab previously developed a mouse model by deleting the gene encoding the catalytic subunit of MCI (Ndufs2) in dopaminergic neurons. The MCI-Park mice manifest a progressive, bilateral, levodopa-responsive parkinsonism. In contrast to the widely used models of PD, where dopamine depletion and motor behavior effects occur rapidly, the staging of pathology observed in the MCI-Park mice mirrors that thought to occur in PD patients, including the axon-first nature of degeneration of SNc dopaminergic neurons. As early conditional deletion of Ndufs2 in dopaminergic neurons could lead to developmental compensations, we created an inducible MCI-Park line. The iMCI-Park mice manifest progressive deficits in nigrostriatal function starting at three months and motoric deficits that parallel the loss of dopaminergic markers in the basal ganglia, beginning with fine motor movements during the prodromal stage that progress into deficits in gross motor skills in parkinsonian stages. Thus, the iMCI-Park mice

provide improved specificity while maintaining the progressive nature of PD, making it an excellent model to study the prodromal period of the disease.

Disclosures: A. Pamukcu: None. **K. Bodkin:** None. **A. Kennedy:** None. **D. Surmeier:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.02/I13

Topic: E.06. Posture and Gait

Support: Aligning Science Across Parkinson's

Title: Three dimensional markerless pose tracking of inducible MCI Parkinsonian mice

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Abstract: Damage to Mitochondrial Complex I (MCI) in Substantia Nigra dopamine (DA) neurons has been shown to result in progressive loss of the DA phenotype and Parkinsonian gross and fine motor deficits. In our investigation, we focused on understanding the motor and behavioral changes in mice with inducible MCI (iMCI) disruption initiated 60 days postnatally (P60). To assess these changes we employed a multi-view recording setup, capturing mice from five angles simultaneously while they performed food -handling and sticker-removal tasks. Our multiview setup had a single bottom-view camera and mirrors positioned at each cardinal direction. We trained two stacked hourglass models in MARS to track the 2D keypoints; one model was trained for the underside view, the other was trained for the mirrors. The datasets to train the 2D models were labeled by workers through AWS ground truth using an interface that we customized to allow for simultaneous labeling of each view. Subsequently we triangulated the 3D position of each keypoint using AniPose. Our study was composed of twenty mice divided into three groups: wild-type, flox/flox cre mice with no deletion (control), and iMCI-Park mice. We recorded each mouse weekly for at least 11 weeks post injection to follow the progression of the deficits.

Disclosures: K. Bodkin: None. **A. Pamukcu:** None. **A. Kennedy:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.03/I14

Topic: E.06. Posture and Gait

Support: National Science Foundation

Title: Gaze-gait coordination during a virtual reality visuomotor stepping task

Authors: *M. MULVEY[1,2], A. T. NGUYEN[3,2,4], J. T. CHOI[5,4];
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Abstract: When navigating complex environments, we must first identify safe footfall locations, and then execute a step sequence to accurately land on successive footfall locations. Virtual reality (VR) provides a safe platform to study visuomotor integration during walking. Practicing visually guided stepping in VR engages both perceptual and motor learning mechanisms, improving stepping accuracy. Vision plays a pivotal role in motor planning, where locomotor sequence learning in young adults has been associated with a change from utilizing feedback to feedforward visual control of stepping. However, the ability to plan and execute complex locomotor patterns is often disrupted in aging. This study examines gaze stability (the ability to steadily focus on objects of interest) and gaze-gait coordination (the coupling between gaze shift and stepping kinematics) in healthy older adults (n=36, mean age 71.8 ± 6.5 years) during a visuomotor stepping task. Participants performed 3 VR stepping trials, where they walked on a treadmill at a normalized speed as 100 targets were projected onto a screen. Participants were instructed to adjust their step lengths so that a blue circle (representing their foot position) landed on successive targets. VR scores were the total number of times the blue circle landed on a target. Gaze-gait coordination was calculated using the time difference between toe off and saccade and between saccade and heel strike. Saccades were defined as gaze velocities greater than or equal to 50 degrees / second. Gaze stability was measured using the variability of the gaze position between saccades. Eye tracking and motion capture data showed that during this VR stepping task, participants initiated a step prior to a gaze shift occurring, meaning that participants began the motor task before visualizing the target which they were planning to hit. Participants continued fixating on the target even after stepping on it. Preliminary results revealed significant temporal adaptations in gaze-gait coordination; specifically, the time from toe off to gaze shift significantly decreased ($p < 0.001$) while the time from gaze shift to heel strike significantly increased ($p = 0.010$) across VR trials. We hypothesize that decreased gaze stability or greater variability in gaze-gait coordination would predict reduced task performance. Further analysis will be conducted to elucidate the relationship between gaze-gait coordination, task performance, and locomotor learning in healthy older adults.

Disclosures: M. Mulvey: None. **A.T. Nguyen:** None. **J.T. Choi:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.04/I15

Topic: E.06. Posture and Gait

Title: Quantifying Gaze Behavior Using Virtual Reality: The Relationship Between Gaze, Mobility, and Cognition in Older Adults

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Abstract: Coordinated eye-head movements (i.e., gaze) are necessary for maintaining a steady visual field while walking. While altered gaze behavior during gait is a critical factor associated with increased fall risk in older adults (Walsh & Snowball, 2023), gaze assessment and training are not part of current fall prevention. The purpose of this study is to 1) quantify gaze function using a virtual reality headset and 2) examine the relationship between mobility level and gaze behavior among healthy older adults with various cognitive capacities. Our long-term goal is to understand how variations in gaze patterns can influence gait and balance control in older adults.A total of thirty-five healthy older adults (13 males, age 71.4 ± 6.8 years) were included in this study. Mobility level was assessed using the Timed Up & Go (TUG). Each participant completed the Montreal Cognitive Assessment (MoCA). Gaze function was assessed based performance in smooth pursuit, saccades, anti-saccades, and the vestibular-ocular reflex (VOR) tests using a virtual reality headset (Neuroflex). The main outcomes of smooth pursuit protocols include mean vergence, the number of saccades, mean error, and the percent head contribution (head free only). VOR provides gain values up & down for the vertical task and right & left gains for the horizontal task, while saccade protocols yield mean vergence, vergence standard deviation, acquisition error, mean latency, and directional accuracy (anti-saccades only). Preliminary findings suggest mean vergence values during smooth pursuit may be a predictor of mobility level in older adults (Pearson's correlation: $p = 0.008$ and $r = 0.548$ for head free, $p = 0.024$ and $r = 0.670$ for head fixed). The relationship between the remaining gaze behavior tests and mobility will also be analyzed. These results can inform future research focused on gaze training for the improvement of mobility.

Disclosures: E. Patterson: None. **M. Mulvey:** None. **J.T. Choi:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.05/I16

Topic: E.06. Posture and Gait

Support: P2CHD086844
R25HD106896

Title: Understanding the Contribution of Altered Functional Brain Connectivity to Poor Balance Control in Chronic Stroke Survivors.

Authors: *K. KUKKAR[1], N. RAO[2], P. J. PARIKH[1];
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Abstract: Balance control is a key indicator of independence in activities of daily living, and its impairment contributes to falls in stroke patients. Stroke causes brain reorganization, which may alter the brain network connectivity. Such alterations can deleteriously affect balance control and generation of effective responses to prevent a fall when the balance is challenged. Remarkably, how the changes in the brain network dynamics following a stroke contribute to impaired balance control remains unknown. We have earlier identified a network of fronto-parietal brain regions related to the control of balance during a challenging balance task in neurotypical adults. In this study, we investigated the stroke-related changes in the brain network dynamics for balance control during a challenging balance task. We recruited fourteen stroke participants with mild-to-moderate severity and ten age-gender matched healthy adults. Participants were instructed to maintain an upright stance in response to balance perturbations on a computerized balance platform. The whole head brain activity was simultaneously measured using electroencephalography (EEG). Stroke participants showed poor performance on the clinical Berg Balance test and the laboratory-based balance task when compared with healthy controls. We found EEG sources of activations in posterior parietal cortices (PPC), dorsolateral prefrontal cortices (dlPFC) and supplementary motor area (SMA) in both the groups. Stroke participants showed lower connectivity between SMA-PPC and higher connectivity between SMA-dlPFC when compared to healthy controls. A stronger functional connectivity between SMA and dlPFC during the balance task might suggest reliance on cognitive function while a weaker SMA-PPC connectivity might suggest poor sensory processing. For stroke participants, a stronger dlPFC to SMA connectivity was associated with a better Berg Balance score. On the other hand, stroke participants with better Berg Balance score showed weaker SMA to PPC connectivity. Our findings suggest that the prefrontal brain areas are recruited to compensate for poor sensory processing. Understanding the associations between altered connectivity and balance score can inform design of interventions aimed at reducing falls in these patients.

Disclosures: K. Kukkar: None. **N. Rao:** None. **P.J. Parikh:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

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Program #/Poster #: PSTR349.06/I17

Topic: E.06. Posture and Gait

Support: P2CHD086844
R25HD106896

Title: Understanding the Effects of Aging on the Brain Network Dynamics for Balance Control

Authors: *M. DADFAR[1], K. KUKKAR[2], P. J. PARIKH[1];
[1]Univ. of Houston, Houston, TX; [2]Hlth. and Human Performance, Univ. of Houston, Houston, TX

Abstract: Poor balance control makes older adults more likely to fall. Deterioration of balance control in older adults is associated with a shift from spinal to supraspinal control of the lower limb muscles. An earlier study in healthy older adults showed higher EEG (electroencephalography) power than young adults in the fronto-parietal brain regions during a challenging balance task. Balance control has been suggested to depend on dynamic interactions between frontoparietal brain regions, especially under challenging environmental conditions. How aging affects the functional connectivity among the frontoparietal brain regions remains to be known. The main objective of the current study was to investigate the effects of aging on the brain network dynamics during a challenging balance task. We recruited ten healthy older adults between 55 and 80 years of age and ten healthy young adults between 18 and 40 years of age. Participants were instructed to maintain balance in response to balance perturbations on a computerized balance platform. We recorded the brain dynamics using whole-head electroencephalography (EEG) while participants performed the task. In young adults, we found EEG sources of activations in bilateral posterior parietal cortices (PPC), anterior cingulate (CG)/supplementary motor area (SMA). In older adults, we found EEG sources of activations in dorsolateral prefrontal cortices (dlPFC), in addition to bilateral PPC and CG/SMA (frontocentral). The recruitment of prefrontal brain areas in older adults might be to compensate for the aging-related impairment in balance control. In older adults, the frontocentral brain region was found to be bilaterally connected with dlPFC and PPC. We observed differences in the strength of these connections. The center of pressure path length measured using the balance platform was greater in older adults when compared to young adults. Our ongoing work is investigating the associations between aging-related changes in the brain's functional connectivity and balance performance in older adults. This knowledge can inform the design of interventions aimed at reducing falls in this population.

Disclosures: M. Dadfar: None. **K. Kukkar:** None. **P.J. Parikh:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.07/I18

Topic: E.06. Posture and Gait

Support: ORF-RE-09-112

Title: Markerless Motion Capture is Sensitive to Greater Mediolateral Balance Impairment During Standing in Stroke

Authors: *S. R. B. A. WIJEKOON[1], S. H. SCOTT[2];
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Abstract: Background Balance improvement is a major target of post-stroke rehabilitation. However, current practices are guided by course clinical assessments based on visual or physical inspection. In the present study, we explored the use of Markerless Motion Capture (MMC) to quantify balance impairment in patients with stroke. **Methods** Patients with stroke (17 ♂, 5 ♀; age=68±14.0 years) were evaluated by a trained physiotherapist using the Berg Balance Scale (BBS), with each task simultaneously recorded using eight time-synchronized Sony RX0II cameras. Healthy controls (24 ♂, 48 ♀; age=57±22.0 years) were recorded performing the same tasks. Raw video data were processed in Theia3D, and the Centre of Mass (COM) signal of the pelvis was extracted for balance assessment. The present study focused on the *unsupported standing task* of the BBS for subsequent analysis. We compared six common measures of the COM sway (Root Mean Square (RMS) distance, range, and mean velocity, in both mediolateral (ML) and anteroposterior (AP) directions) between stroke and control groups using cumulative distribution functions. Patients with values exceeding the 95th percentile of the controls were identified as impaired. **Results and Discussion** Although magnitudes of each measure were observed to be higher in the AP direction, patients with stroke were identified with more ML than AP impairments in both RMS distance (41.0% vs. 13.6%) and range (41.0% vs. 27.3%). In addition, significant negative correlations were observed between total BBS score and RMS distance (r_s = -0.761, $p < 0.0001$) as well as range (r_s = -0.786, $p < 0.0001$) in the ML direction. These results likely reflect the presence of hemiparesis (one-sided weakness) in stroke, which primarily impacts frontal-plane balance. Conversely, impairments in mean velocity were more common in both ML (63.6%) and AP (68.2%) directions and were moderately negatively correlated to the total BBS score (ML: r_s = -0.653, $p = 0.001$ | AP: r_s = -0.647, $p = 0.001$). The greater number of impairments may stem from increased compensatory micro-adjustments in patients with stroke that may not impact measures of overall sway and are less visually discernible, potentially explaining the diminished correlations with the total BBS score. **Conclusions** The present research supports the use of MMC in a stroke population, demonstrating that objective differences in postural control can be identified purely from standing. Its minimal setup time and portability present exciting potential over existing technology to provide a clinically accessible assessment tool that can better monitor post-stroke recovery and individualize rehabilitation strategies.

Disclosures: S.R.B.A. Wijekoon: None. **S.H. Scott:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.08/I19

Topic: E.06. Posture and Gait

Title: Neural networks implicated in gait apraxia

Authors: *Z. FIORE[1], O. BENZLEY[1], F. SCHAPER[2], M. FERGUSON[2], J. A. NIELSEN[3]; [1]Neurosci., Brigham Young Univ., Provo, UT; [2]Brigham and Women's Hosp., Harvard Med. Sch., Boston, MA; [3]Psychology, Brigham Young Univ., Provo, UT

Abstract: Gait apraxia is a type of apraxia that affects lower limb use in walking. It is characterized by difficulty initiating gait, freezing of gait, and other gait disturbances that cannot be attributed to complications affecting sensory, motor, or cerebellar function, psychiatric disease, nor ataxia. Gait apraxia symptoms often present following strokes, encephalitis, tumors or acquired brain injuries. Previous research relying only on direct lesion sites has indicated that gait apraxia may be associated with lesions in the frontal lobe, basal ganglia, supplementary motor area and cingulate cortex. However, the specific cerebral location has been debated with minimal research done on the symptom's implicated neural circuits. The purpose of this study is to determine the networks in the brain that are involved in the pathophysiology of gait apraxia. To determine this, we used the lesion network mapping method. A systematic literature review was performed, with specific inclusion criteria, to find case studies of patients presenting with gait apraxia stemming from acquired brain injury (n=30). Lesion network mapping analysis (Fox et al., 2018) was performed on 30 cases with a large cohort of healthy control resting-state scans (n=1000). This method investigates brain regions functionally connected to the lesion sites rather than the case study lesion sites exclusively. We found that 83% of cases (25/30) were functionally connected to the posterior cingulate cortex. This connectivity pattern was specific to gait apraxia compared to lesions causing other neurological conditions. The identified location seems to be a part of the frontoparietal network. The posterior cingulate cortex has not frequently been linked with gait apraxia and its association with movement is generally not well understood. Further research is necessary to determine the mechanism of how these networks interact in contributing to gait apraxia. These findings can help clinicians more accurately understand and more effectively treat gait apraxia. They can also potentially provide insight into apraxia as a whole.

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Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

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Program #/Poster #: PSTR349.09/I20

Topic: E.06. Posture and Gait

Support: U.S. Army Medical Research and Materiel Command under work unit numbers N1817 and N2025
Traumatic Brain Injury Center of Excellence,HT0014-22-C0016

Title: A preliminary study on the effect of dual tasking on gait in military service members after a mild traumatic brain injury

Authors: C. DAQUINO[1,2], T. WHITTIER[1,2], H. RIZEQ[1,2], *W. ZHENG[1,2], M. ETTENHOFER[3,4], S. I. GIMBEL[3,4], L. HUNGERFORD[3,4], P. SESSOMS[1];
[1]Naval Hlth. Res. Ctr. (NHRC), San Diego, CA; [2]Leidos Inc., Reston, VA; [3]Naval Med. Ctr. San Diego, San Diego, CA; [4]GDIT, Chula Vista, CA

Abstract: Mild traumatic brain injury (mTBI) is common among service members (SM) and can lead to motor system disruptions and gait abnormalities that adversely affect quality of life. Dual tasking assesses cognitive-motor functioning and identifies mTBI-related gait deficits. However, limited research has explored the efficacy of simulated military-relevant tasks in detecting these instabilities. We hypothesized that mTBI participants would display abnormal gait patterns, evaluated through step length and width, during a dual task. Data were collected from 14 SM, 8 with a chronic mTBI (7 M/1 F; age: 32.8 ± 6.2 yr) and 6 controls (4 M/2 F; age: 28.8 ± 6.9 yr), who completed cognitive-motor tasks in an immersive virtual reality environment. Participants walked at 0.75 m/s and were instructed to recognize, aim, and shoot avatars on a screen depending on if the current avatar was the same or different from the previous one (one back). The second task increased cognitive load as battlefield radio chatter was broadcast and participants orally responded to specific chatter cues (dual task). Motion capture data were collected at 120 Hz using optical motion capture (Motion Analysis Corp., Rohnert Park, CA) from markers placed on participants' heels. The first 200 steps were used to calculate mean values of step length and width of the right side. Statistical differences were analyzed using an independent samples t-test and 2-way repeated measures ANOVA ($\alpha = 0.05$). On average, chronic mTBI participants displayed greater step length than controls in the one back (52.9 ± 5.5 cm vs 44.7 ± 9.5 cm) and dual task (53.7 ± 3.92 cm vs 45.9 ± 11.6 cm) and larger step widths (one back = 16.8 ± 3.9 cm vs 15.1 ± 3.2 cm, dual task = 16.0 ± 4.1 cm vs 14.1 ± 2.6 cm). Though not statistically significant (step length one back $p = 0.06$, dual task $p = 0.1$; step width one back $p = 0.39$, dual task $p = 0.33$), large effect sizes were observed for step length (one back $g = 1.04$, dual task $g = 0.91$) and moderate effect sizes for step width (one back $g = 0.5$, dual task $g = 0.6$), indicating mTBI-related gait changes. Significant differences in gait were not observed within groups and task type (step length $p = 0.9$, step width $p = 0.8$) or within the overall group (step length $p = 0.06$, step width $p = 0.4$). Contrary to our hypothesis, task type did not significantly impact step length or width for either population. Further analyses will aim to address these findings by using a larger sample size of mTBI patients with balance deficits and evaluating response time or shooting accuracy to assess task prioritization in each group. Future research will continue to unveil the interplay between cognitive demands and motor function in military populations.

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Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

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Program #/Poster #: PSTR349.10/I21

Topic: E.06. Posture and Gait

Title: The effect of aging on Cortical Control of Static and Dynamic Balance: A Systematic Review and Meta-analysis

Authors: Y. HU[1], R. PATEL[2], N. KELEKAR[3], ***M. E. HERNANDEZ**[4];
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Abstract: The number of individuals over the age of 65 has been increasing over the recent years which means a rise in individuals with decrements in control of balance and increased falls. In this meta-analysis, we aimed to determine the changes in the spatiotemporal dynamics of brain activity when mechanical perturbations, cognitive tasks, and modulation of sensory inputs challenge static and dynamic balance control between younger and older adults. We also studied how these changes relate to their balance capacity such as postural sway, fall risk, and overall balance abilities. Participants above the age of 65 were categorized as the older adult (OA) cohort versus younger adult (YA) cohort. We focused on articles that included healthy OA cohorts free of neurological disorders. The data analyzed was independent of sex as the males and females were grouped together when running the data through R-studio. Data was collected from PubMed, Scopus, Web of Science, CINAHL, IEEExplore, and Compendex. Outcome measures included oxygenated hemoglobin (HBO2) and deoxygenated hemoglobin (HHB) levels using fNIRS when performing tasks such as standing and balancing simultaneously (SB), standing while performing a cognitive task (SC), single walking (W), walking while performing another task (DT), and walking while overcoming an obstacle (WO). The only brain area included in this analysis was the prefrontal cortex (PFC). Fixed effect model and random effects models were used to examine the effects of cohort, task, and their interactions on HBO2 and HHB levels. The HBO2 levels significantly increased in the SB condition in healthy OA compared to the YA ($p<0.01$) in the overall, left, and right regions of the PFC. Conversely, the HHB levels decreased in this condition in OA compared to the YA in the same regions of the PFC ($p<0.01$ and $p<0.05$). The HBO2 levels also increased in the W condition in healthy OA compared to the YA ($p<0.01$ and $p<0.02$). Another condition where the HBO2 levels increased in OA compared to YA is the DT condition ($p<0.01$ and $p<0.05$). Oddly, the HHB levels in the DT condition did not produce any significant results ($p>0.50$). In the SC task, the HBO2 levels did not produce a significant result ($p>0.50$) as well. Lastly, similar to the SC task, HBO2 levels in the WO condition did not show consistent results ($p>0.10$). Aging may increase PFC activation when completing specific static and dynamic tasks such as SB, W, and DT tasks. There are still some balancing tasks that did not demonstrate a statistical significance between older and younger adults which merits future investigation to determine if cortical control of all types of balance is truly affected by aging.

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Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.11/I22

Topic: E.06. Posture and Gait

Title: Benefits from left frontal aslant tract stimulation do not degrade postural sway in people with Parkinson's disease

Authors: T. M. GAUSS[1], F. TABARI[2], K. JOHARI[2], *J. M. HONDZINSKI[1];
[1]Kinesiology, [2]Communication Sci. and Disorders, Louisiana State Univ., Baton Rouge, LA

Abstract: Individuals with Parkinson's disease (PD) experience motor dysfunction of gross and fine motor skills. The well-known deficits in balance and speech for this population can provide these individuals with daily problems affecting their quality of life. Invasive medical interventions and/or medicines for people with PD often do not address speech and balance dysfunctions, simultaneously, and can accompany unpleasant side effects. Finding noninvasive treatment protocols without side effects can offer an attractive option for many with PD. Previous research showed that High-Definition transcranial Alternating/Direct Current Stimulation (HD-tACS/tDCS) to the left frontal aslant tract (FAT) improved speech performance in some populations, but its impact on speech and standing balance in people with PD remain unknown. We examined whether 25 min of HD-tACS/tDCS over the left FAT improved standing postural sway compared to a sham-stimulated state. Participants performed three trials of static stance in eyes opened and eyes closed for stimulation and sham-stimulation conditions on two days separated by at least one week. In one visit, participants received a sham stimulation as a control condition, while in the other visit participants received actual stimulation. Weekly order was counterbalanced across participants. Participants stood without shoes as still as possible with a narrow base of support for 30 sec on an AMTI force plate (100 Hz) to determine center of pressure (CoP)-based postural sway variables of interest which included dynamic measures of sample entropy, an indicator of more automated control. Participants completed three alternating trials of eyes open and eyes closed standing balance for a total of six trials. Repeated measures ANOVA revealed an increase in velocity and path length of CoP with eyes closed compared to eyes open in both sham and stimulation conditions. The difference in postural sway variables when vision was impacted adds to the existing literature that vision plays an important role in balance, especially in older adults, including those with PD. Results showed no difference in postural sway variables between the sham and actual stimulation conditions. These data reveal that a single stimulation of the left FAT apparently does not improve or degrade postural sway in PD. Multiple HD-tACS/tDCS stimulation sessions of the left FAT may be needed to impact balance. Results provided evidence that the use of HD-tACS/tDCS as a noninvasive treatment intended to improve speech in PD does not negatively impact balance in this population.

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Poster

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Program #/Poster #: PSTR349.12/I23

Topic: E.06. Posture and Gait

Support: ERC-2012-SyG_318987
DFG-BL1812_1
JHS AddOn Fellowship

Title: Cell-type specific modulation of cortical circuits ameliorates Huntington's Disease phenotypes

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Abstract: The dysfunction of the corticostriatal circuit is central to the development and progression of the neurodegenerative movement disorder Huntington's disease (HD). Previous studies have shown HD-related changes in cortical excitatory neuron activity, possibly related to a loss of inhibitory control through local inhibitory neurons. Despite its relevance, the involvement of specific cortical excitatory and inhibitory neuronal populations in HD remains largely unexplored. To dissect the contributions of major cortical neuron subtypes, we performed longitudinal *in vivo* 2-photon calcium imaging of excitatory corticostriatal projection neurons (CPN) as well as inhibitory parvalbumin (PV), somatostatin (SST) and vasoactive intestinal peptide (VIP) populations in the R6/2 HD mice and wildtype littermate controls. Neuronal activity and mouse behavior were monitored over the presymptomatic and symptomatic phases of disease progression. Using pose estimation and behavior classification, we show that gait and behavioral state dynamics in R6/2 mice progressively diverge from healthy controls. These abnormalities coincided with aberrant activity of distinct inhibitory neuron types. Specifically, R6/2 mice showed intensifying SST hyperactivity and VIP hypoactivity over disease progression, while CPN activity was markedly reduced during motor output in symptomatic animals. We show that optogenetic stimulation of VIP interneurons during movements restored healthy VIP activity levels and partially normalized CPN activity. Importantly, VIP stimulation also improved motor learning and thereby delayed the progression of motor symptoms in R6/2 mice. Our results indicate that HD affects cortical circuits in a cell-type specific manner and demonstrate the potential for targeted therapeutic intervention.

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Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.13/I24

Topic: E.06. Posture and Gait

Support: ANR-15-IDEX-0003 FRAGILIFE

Title: Targeting a specific motor control process reveals an age-related compensation that adapts movement to gravity environment

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Abstract: As the global population ages, it is crucial to understand sensorimotor compensation mechanisms that allow older adults to remain in good physical health, i.e. underlying successful aging. Although age-related compensation has long been conceptualized and despite important research effort in varied gerontological subfields, behavioral compensatory processes and their underlying neural mechanisms remain essentially chimeras. This study investigates age-related compensation at the behavioral level. It tests the basic hypothesis that age-related compensatory processes may correspond to an adaption process that changes movement strategy. More specifically, we focused on the ability of younger (n = 20; mean age = 23.6 years) and older adults (n = 24; mean age = 72 years) to generate movements that are energetically efficient in the gravitational environment. Previous results, from separate studies, suggest that aging differently alters energy efficiency in arm movement and whole-body movement tasks. With aging, energy efficiency seems to remain highly functional in arm movements but was shown to decrease in whole-body movements. Here we built on recent theoretical and experimental results demonstrating a behavioral process that optimally adapts human arm movements to the gravitational environment. Analyzing phasic muscle activation patterns, previous studies provided electromyographic measurements that quantified the output of an optimal strategy using gravity effects to discount muscle effort. Using these measurements, we probed the effort-minimization process in younger and older adults during arm movement and whole-body movement tasks. The key finding demonstrates that aging differently alters motor strategies for arm movements vs whole-body movements ($F(1,42)= 5.48$, $P=2.44E-02$, $\eta 2=0.120$). Older adults used gravity effects to a similar extent as younger ones when performing arm movements (older adults, mean ± SD, a.u.: -10.7 ± 5.6, 95% CI: [-8.4;-13.0]; younger adults, -11.4 ± 3.6, [-9.8;-13.0]), but to a lesser extent when performing whole-body movements (older adults, -9.7 ± 3.2, [-8.0;-11.5]; younger adults, -15.6 ± 3.3, [-14.1;-17.0]). These results provide clear experimental support for an adaptation strategy that down-regulates effort minimization in older adults. This adaptation would reflect a compensation rather than a sole deterioration as the optimal planning

capability is unimpaired in older adults during arm movements. Additional experiments are being performed using a gas-analysis system to provide more direct support to this hypothesis.

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Poster

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Topic: E.06. Posture and Gait

Support: SFN Grant 1815506

Title: Motor control of the foot during obstacle crossing in natural and virtual environments

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Abstract: Virtual Reality (VR) is a promising tool for clinical and therapeutic use. One fundamental motor skill that has been targeted for assessment and rehabilitation in VR is locomotion, with a particular emphasis on obstacle crossing (Borrego et al. 2016). When negotiating obstacles, individuals rely heavily on visual feedback about the environment and their body. However, accurate representation of the lower limbs in VR remains a challenge. The aim of this study was to determine how leading and trailing leg toe clearance is impacted when stepping over obstacles in a natural environment with full vision of the surroundings and body and VR where visual feedback about the surroundings is synthetic and there is no representation of the body. Young adults (n=12) walked across an instrumented gait mat under two visual conditions: (i) natural environment/normal vision (NE), and (ii) virtual reality/no representation of the lower body (VR). Participants stepped over an obstacle that was positioned mid-way along the length of the mat. Obstacle height was manipulated such that participants stepped over obstacles of five different heights (0, 3, 7, 12, 17 cm). Repeated measures ANOVAs were performed to examine the effect of the two visual conditions and five obstacle heights on leading and trailing leg toe clearance. Main effects for block height and visual condition were found for leading leg ($p<0.001$) and trailing leg ($p<0.001$). The interaction between visual condition and block height was not significant for either measure. Leading leg toe clearance increased as block height increased, however, toe clearance between the 7, 12 and 17 cm blocks heights were not significantly different. Trailing leg toe clearance was smaller at the 0 cm height (8.17 ± 0.64) than all other block heights which were not significantly different than each other. Finally, leading leg

toe clearance was greater in VR (16.26±0.68) than the natural environment (13.52±0.65). Results of this study suggest that walking in VR causes individuals to employ larger safety margins with the leading toe when clearing an obstacle. These findings support previous findings from our team indicating a more conservative gait approach in VR. Leading leg toe clearance heights were also influenced by obstacle height in a non-linear fashion with clearance height increasing linearly for the three smaller obstacles, but reaching a plateau at the 7 cm obstacle height. In contrast, these conservative clearance strategies did not extend to the trailing toe, suggesting that online proprioceptive feedback can be used to adjust toe clearance height for the trailing limb.

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Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.15/I26

Topic: E.06. Posture and Gait

Support: University of Michigan Elizabeth Crosby Faculty Award

Title: The Relationship between Upper Extremity and Balance Function in Mild Multiple Sclerosis

Authors: *Q. BAO[1], D. KINNETT-HOPKINS[2], S. H. BROWN[2];
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Abstract: The performance of reaching and object manipulation tasks while standing requires the integration of visual, vestibular, and somatosensory feedback to maintain an upright posture. Impairments in both balance and upper limb movements have been documented in persons with multiple sclerosis (MS), yet clinical assessment of functional disability focuses heavily on deficits in postural control. To what extent balance impairments may be associated with degraded arm and hand function has not been well studied, particularly in those with mild MS symptoms. Upper limb and balance function was assessed in 15 participants with MS (mean age 51.9 ± 10.1y) and 15 sex-and-age matched healthy controls (mean age 51.3 ± 10.1y). Upper limb function of the dominant and nondominant arms was assessed using the nine-hole peg test (NHPT), Jebsen Taylor Hand Function Test (JTHFT), and a novel reach, grasp and release test using a modified Connect 4 ® board (Con4). Balance was measured using the Mini-BESTest and a force platform (BTrackS Balance Tracking System) which included vision/no vision and firm/compliant surface conditions. MS participants were considered mild according to the Patient-Reported Expanded Disability Status Scale (median: 2.5, range: 1-3). In the MS group, reduced dexterity was only seen for the nondominant hand (NHPT: $p=0.04$, Con4: $p=0.03$) while the JTHFT detected no differences in hand function. Mini-BESTest scores did not differ between groups. Declines in balance control based on sway path length and velocity (eyes open $p<0.01$, eyes closed $p\leq0.01$) were observed regardless of surface compliance. Removal of vision in the

MS group when standing on a firm surface led to a 45% increase in sway compared to a 20% increase in the control group. Sway during the no vision/compliant surface condition increased similarly in both groups. Force platform measures were moderately to strongly correlated with all upper limb assessments and for both arms (correlation coefficient ranges: .64 -.75, p value ranges: .04-.003). The Mini-BESTest scores correlated only with nondominant hand measures ($p<0.03$). The results of this study demonstrate that, in persons with mild MS, standard clinical assessments of balance impairments may not be sufficiently sensitive to detect impaired postural control. Increased reliance on vision when standing on a firm surface may reflect impaired utilization of somatosensory and vestibular feedback (Kanekar et al 2014; Riem et al 2021). Clinically, the observed associations between postural control and dexterity measures underscore the importance of evaluating upper limb function when balance deficits are reported in MS.

Disclosures: Q. Bao: None. **D. Kinnett-Hopkins:** None. **S.H. Brown:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.16/I27

Topic: E.06. Posture and Gait

Support: VA I0RX003115 (E3115R)

Title: Walking and dynamic balance parameters during 90-degree turns in older adults with decreased somatosensation

Authors: *E. BINMULAYH[1,2,3], C. W. SWANSON[2,4], S. WINESETT[2,5], B. BORGIA[3], A. GRUBER II[2], D. K. ROSE[3,2,7], A. J. WOODS[6], R. D. SEIDLER[3], D. J. CLARK[8,4];
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Abstract: Turning while walking is a common complex task requiring dynamic stability, which can be challenging for older adults due to declines in motor and sensory function. Turning-related falls are eight times more likely to result in hip fractures than falls during linear walking. This study aims to assess dynamic stability during 90-degree turns in older adults with two different levels of somatosensory function. Fifty older adults (age: 74.5 ± 7.5; 36 males) with mild to moderate mobility limitations performed straight walking and 90-degree turns over a pressure-sensitive walkway to obtain center of pressure (COP) and spatiotemporal data. Participants were categorized into two groups based on the ability to consistently detect touch sensation from 2 grams Semmes-Weinstein monofilament (G1: n=32; age=73.1 ± 5.8; 22 males) or not (G2: n=18; age=77.1 ± 9.4; 14 males). Two sample t-tests and repeated measures ANOVA were used for between and within-group analyses. Compared to G1, G2 completed the turns with

a significantly higher number of steps (p=.004; 95%CI: -0.82 to -0.2) and longer double support time (p=.008; 95%CI: -.01 to -.06). When comparing turning to straight walking, differences in G2 showed that turns had slower COP velocity ($F_{2,103}$= 3.9; p=.02), higher COP path sway ($F_{2,103}$=7.4; p=0.001), shorter step length ($F_{2,103}$=25; p<.0001), and longer double support time ($F_{2,103}$=13.2; p<.0001). Similar findings were observed for G1; however, there was no significant difference in COP velocity. The reduced COP velocity for G2 occurred in early-, mid-, and late-turn phases ($F_{3,102}$=7.5; p=.0001), while in G1, the reduction was less pronounced and observed only in the late-turn phase ($F_{3,189}$=3.7; p=.01). Both groups had increased COP path sway in the mid-turn phase (p<.0001). Reduced step length in G2 occurred during the mid-turn phase ($F_{3,102}$=17.3; p<.0001), which was not observed in G1. G2 had increased time of double support in late and mid-turn phases ($F_{3,102}$=12.7; p<.0001), which for G1 was less pronounced and only observed in late-turn phase ($F_{3,187}$=5.4; p=.002). The results indicate that, compared to linear walking, turning tasks showed significantly slower COP velocity, increased number of steps, reduced step length, and extended double support times in older adults with reduced somatosensation. The findings support that somatosensory impairments in older adults may contribute to reduced dynamic stability with turning performance, providing valuable insights that justify future studies to address the implication of somatosensory impairments on turning performance, as well as rehabilitation aimed at enhancing independent mobility and fall prevention.

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Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.17/Web Only

Topic: E.06. Posture and Gait

Support: PRONACES-CONACYT 194171
BUAP-CA-288

Title: Effect of 4-aminopyridine on gait pattern in taiep rat, a model of tubulinopathy leukodystrophy

Authors: *D. MARTÍNEZ MARTÍNEZ[1], C. CORTES[2], V. PIAZZA[3], J. R. EGUIBAR, Sr.[4]; [1]Inst. de Fisiología, Benemérita Univ. Autónoma de Puebla, Puebla, Mexico; [2]Inst. of Physiol., B. Univ. Autonoma de Puebla, Puebla, Mexico; [3]Ctr. de investigaciones en óptica A.C., León, Mexico; [4]Behavioral Neurophysiol., Benemerita Univ. Autonoma De Puebla, Puebla, Mexico

Abstract: Effect of 4-aminopyridine on gait pattern in the *taiep* rat, a model of tubulinopathy leukodystrophy.D. Martinez[1], J. Ahumada[1], C. Cortes[1], V. Hernandez[3], V.

Piazza[4], Jose R. Eguibar[1-2].*[1]Institute of Physiology, Benemérita Universidad Autónoma de Puebla. [2]International Office, Benemérita Universidad Autónoma de Puebla. [3]Department of Chemical, Electronic and Biomedical Engineering. Division of Sciences and Engineering, University of Guanajuato, León, Gto. [4]Center for Research in Optics, León, Gto., Mexico.*Tubulinopathies are diseases caused by a mutation in the tubulin genes, being the affected gene *tubulin b4a*, causing hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC), with equal MRI features in adult male *taiep* rats. This mutant was obtained from a spontaneous mutation in the selection process to obtain a high-yawning subline from Sprague-Dawley and it is the only available rodent model of H-ABC with long life expectancy. *Taiep* is the acronym for the progressive motor signs tremor, ataxia, immobility, epilepsy, and paralysis. The *taiep* rat is ideal for testing new therapeutic options for H-ABC disease, for which there is not available treatment options until now. 4-aminopyridine (4-AP) is a potassium channel blocker of Kv 1.1 and 1.2 that increases the efficiency of synaptic transmission. This study aimed to assess the effects of systemic administration of 4-AP on gait pattern in 3-month-old male *taiep* rats. We evaluated intraperitoneal administration of 1 and 1.5 mg/Kg doses of 4-AP. Gait evaluations were done in CatWalk^{TM} system (Noldus Technologies, The Netherlands). Our results showed that 1 and 1.5 mg/kg of 4-AP improved gait coordination (Kruskal-Wallis $P<0.001$, followed by Dunn's test $P<0.05$). Additionally, with a significant decrease in the duration of the swing phase ($P<0.001$), as well as the stance phase in the forelimbs ($P<0.05$) and in the hindlimbs ($P<0.001$). In conclusion, the administration of 4-AP improves the gait pattern by accelerating the phases of the gait cycle and increasing the coordination and cadence that concomitantly reduces ataxia. In base of this results, 4-AP could be the base for new therapeutics for leukodystrophies or even multiple sclerosis.
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Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.18/I28

Topic: E.06. Posture and Gait

Title: Effects of lateral postural perturbation on dynamic balance in people post-stroke

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Abstract: People post-stroke have a higher risk of falling due to deficient balance and gait, and consequences of falls in stroke patients are much greater than that in healthy older adults.

Maintaining dynamic balance during locomotion is a major challenge in people post-stroke. The goal of this proposed research was to explore motor adaptation to a mediolateral postural perturbation during walking in people post-stroke. Three individuals who had a stroke visited the lab once to complete two experimental sessions (i.e., cross-over design, session order randomized). Each session had a 11-min treadmill walking with either “lateral postural perturbation” or “no lateral postural perturbation” (1-min baseline, 8-min adaptation to intervention, & 2-min post-adaptation). Participants showed enhanced muscle activation of the paretic hip abductors and adductors immediately after the treadmill walking with lateral postural perturbation, whereas no enhancement after the treadmill walking with no lateral postural perturbation. These enhanced abductor and adductor muscle activities were retained until the late post-adaptation period. Further, walking with lateral postural perturbation resulted in improved lateral weight transfer toward the paretic side and dynamic balance of the paretic leg. In conclusion, walking with lateral postural perturbation may increase lateral weight transfer toward the paretic leg, enhance forced use of the paretic leg, and consequently improve dynamic balance. Applying mediolateral postural perturbation toward the paretic side during walking can be used as a novel intervention strategy to improve motor control of the paretic leg and dynamic balance during walking in people post-stroke.

Disclosures: N. Macias: None. **S. Park:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

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Topic: E.06. Posture and Gait

Support: NIH T32 HD007414 to AJB
Women's Initiative Network at Kennedy Krieger
Joey’s Foundation
FM Kirby Foundation

Title: Targeting self-initiated postural control mechanisms in children with cerebral palsy to optimize balance

Authors: *N. M. HILL[1,2], A. J. BASTIAN[1,2], J. L. KELLER[1,2];
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Abstract: Postural control mechanisms provide the body stability needed for a child to freely engage objects in their environment with their arms. During development, postural control is gained from the head down as motor output and sensory input integrate to refine (e.g., strengthen, prune) the neural connections necessary for specific control of the body. Interruptions to this developmental process, such as from the assorted neurological injures that result in cerebral palsy, can lead to missed developmental milestones and long-term physical impairment.

It is known that extensive practice with self-initiated balance perturbations facilitates the acquisition of mature postural control. This experience is largely absent for children with cerebral palsy (CP), and participation in rehabilitation provides a supported context to address motor impairments using therapeutic activities. The extent of balance practice that children with CP receive in clinical care is limited by constraints to time (1 hour/week) and personnel (1 therapist for handling/activity facilitation). Additionally, while children would benefit most from targeted rehabilitation during the time window when neural circuits are still developing, this overlaps with the period when attention spans are short and engagement in therapy can be low. This low dose of balance practice may significantly contribute to slower and less complete postural control acquisition. Virtual reality-based therapies are available to adults to augment therapeutic dose but are not as well suited for young children. We have shown that young children are engaged in gamified therapy using our recently developed touch-screen interactive PediaCORE Aiding Distanced and Accessible Physical Therapy (ADAPT) System. We hypothesize that ADAPT not only engages young children but also supports them in achieving an increased dose of the desired therapeutic activity. Here, we present results from 12 children aged three to six years old with CP and compare gamified therapy with the ADAPT system to typical therapy activities using physical objects. We explored the dynamic range of arm movement and weight shifts between the therapy delivery approaches using video recordings, wearable sensors, and a pressure mat. While participants had similar time durations of active engagement, they completed more movements to the screen during the ADAPT game (mean 43 counts/min) than engagements with objects during typical therapy (mean 16 counts/min). Continued analysis will investigate contrasts in balance control performance elicited during the two therapy paradigms and allow us to target specific mechanisms with the appropriate intervention.

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Poster

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Program #/Poster #: PSTR349.20/I30

Topic: E.06. Posture and Gait

Support: U01AG061389
FG -2207-40150
T32AG062728
S10 OD021726

Title: Differential association of cerebrospinal fluid-interstitial fluid exchange and walking speed in young and older adults

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Abstract: Background: Exchange of cerebrospinal fluid and interstitial fluid (CSF-ISF exchange) via the glymphatic system helps maintain brain health by clearing out neurotoxic materials. A novel method has emerged to potentially quantify this function as diffusion ALong the Perivascular Space (ALPS; Taoka et al., 2017. *Jpn J Radiology*) with diffusion-weighted MRI. ALPS-index is correlated with intrathecal contrast enhanced MRI, which is considered the gold standard for assessment of CSF-ISF exchange (Zhang et al., 2021. *Neuroimage*). The unique orientation of the fibers adjacent to the medullary veins allows the calculation of diffusivity in the direction of the perivascular space. Characterizing CSF-ISF exchange in older adults across a broad walking spectrum may provide insight into the mechanisms underlying variable walking decline in older adults. The objectives of this study were to: (1) identify differences in CSF-ISF exchange in younger adults and older adults with high and low physical function, and (2) determine whether CSF-ISF exchange is associated with walking speed. Methods: This study included 21 young adults, 29 older adults with higher physical function, and 56 older adults with lower physical function. Structural T1 and diffusion-weighted (64-direction) magnetic resonance imaging scans were acquired. CSF-ISF exchange was quantified by the ALPS equation; the mean of the x-axis diffusivity in the projection fibers and in the association fibers was normalized by the mean of y-axis diffusivity in the projection fibers and z-axis diffusivity in the association fibers (ALPS index = mean[Dx*proj*, Dx*assoc*] / mean[Dy*proj*, Dz*assoc*]). Walking speed was assessed with a 400-m walk at preferred pace. Group differences in ALPS-index were assessed with a one-way ANOVA. Association between ALPS-index and walking speed in young and old age groups was assessed with linear regression.Results: Young adults had a higher ALPS-index compared to older adults with higher and lower physical function, but there were no differences between older adult groups. Walking speed was associated to the ALPS-index and there was a significant interaction of age groups in this association. Higher ALPS-index was associated with higher walking speed in older adults, whereas higher ALPS-index was associated with slower walking speed in younger adults. Additional data analyses are ongoing.Discussion: CSF-ISF exchange may be a compensatory mechanism for older adults to maintain higher walking speeds. In young adults, higher CSF-ISF exchange was associated to slower walking speeds, which may suggest neuromechanistic differences underlying walking between age groups.

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Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.21/I31

Topic: E.06. Posture and Gait

Support: CIHR Grant 173526. Canada Research Chairs CRC-2019-00290

Title: Spatio-temporal gait parameters provide insight into the function of the corticospinal tract in multiple sclerosis

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Abstract: Gait disturbance may serve as an indicator of neurodegenerative disease, yet the specific spatio-temporal parameters that best reflect dysfunction in the corticospinal tract (CST) remain unclear. The objective of this study was to identify the spatio-temporal parameters that best reflect CST dysfunction in individuals with multiple sclerosis (MS). This cross-sectional study was conducted in a single visit. Participants completed a transcranial magnetic stimulation (TMS) and a gait analysis test. The inclusion criteria were: age ≥ 18 years, definitive diagnosis of MS according to McDonald criteria, ability to walk at least 100 meters, no contraindications to TMS, and inactive and relapse-free disease for ≥ 3 months. We assessed CST function with TMS and spatio-temporal parameters during fast-paced walking with an electronic walkway. We used Pearson correlation analysis to examine the relationships between TMS data (active motor threshold [AMT], inhibitory recruitment curves [iREC], excitatory recruitment curves [eREC]) and gait data (spatial, temporal and balance). In the subsequent three-stage regression analysis, we included only those gait parameters that demonstrated a significant association with CST. Stepwise regression identified those variables predictive of CST. In the final model, we entered all significantly predictive gait parameters in stepwise regression. Of the 105 participants, 27 were excluded because they did not meet the inclusion criteria. The mean age of 78 participants (58 female and 20 male) was 47.91 years. The median EDSS score was 2.0. All spatial and temporal parameters were significantly associated with AMT and iREC ($p < 0.05$). All spatial and temporal parameters except stride width were significantly associated with eREC ($p < 0.05$). In the final regression analysis, the sole gait parameter that predicted AMT was single support center of pressure distance (Δr^2: 0.258). The sole gait parameter that predicted eREC was total double support (Δr^2: 0.133). The gait parameters that predicted iREC were stride width (Δr^2: 0.063) and stride duration (Δr^2: 0.305). We present new evidence of potential spatio-temporal gait biomarkers suggesting CST damage. These findings support that maintaining the functionality of gait, especially stability, is associated with CST function and is a sensitive indicator of neurodegeneration. The usefulness of these biomarkers should be assessed in future longitudinal studies and interventional clinical trials.

Disclosures: F. Bilek: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CIHR Grant 173526. Canada Research Chairs CRC-2019-00290. **A.R. Chaves:** None. **M. Ploughman:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CIHR Grant 173526. Canada Research Chairs CRC-2019-00290.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.22/I32

Topic: E.06. Posture and Gait

Support: Restore Center P2C (NIH P2CHD101913)

Title: Gait-based biomarkers of recovery during inpatient therapy after stroke from markerless motion capture

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Abstract: Gait impairments are a common treatment focus during both inpatient and outpatient rehabilitation. Despite the importance and prevalence of gait, beyond walking speed, logistical barriers mean that gait is rarely quantitatively measured in these settings. Because this data is rarely collected, there have been limited opportunities to quantitatively track changes in gait through therapy and develop novel impairment measures. Here we describe work on both the logistical barriers to gait analysis and on developing new metrics using this data. Formal gait analysis and even instrumented gait mats are prohibitively expensive and time consuming for routine care. Recent advances in markerless motion capture are poised to substantially reduce this barrier. We developed a markerless motion capture (MMC) system and biomechanical analysis pipeline designed to easily integrated into clinical care. A web-based interface allows capturing MMC data from multiple calibrated and synchronized network-connected cameras in our hospital. A novel differentiable biomechanics approach that leverages recent machine-learning oriented biomechanical frameworks allows us to end-to-end optimize trajectories collected with this, including to infer joint torques. We used this system to perform gait analysis on a people after an acute stroke at the beginning and end of their rehabilitation. As anticipated, spatiotemporal gait parameters differed in the participants with a history of stroke and improved over rehabilitation. The system could also detect the classical features of a hemiparetic gait, such as foot drop and circumduction. We trained a neural network to map the temporal sequence of joint angles into a high dimensional embedding using a contrastive loss. Instead of using typical augmentations, we treated different short time samples of walking as different views for our contrastive loss. The key goal of self-supervised learning approaches like contrastive learning is to learn a representation that is useful for downstream tasks, and we found this was true for our learned embedding. In a cross-validated framework, we found this learned embedding allows a simple linear classifier to distinguish diagnosis and laterality of impairments. We also found the distance in embedding space between stroke survivors and the average health control reduced over the course of inpatient rehabilitation. In conclusion, MMC allows more routine quantitative characterization of gait during rehabilitation. This creates many opportunities, including novel data-driven approaches to develop gait-analysis based biomarkers.

Disclosures: R. Cotton: None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.23/I33

Topic: E.06. Posture and Gait

Support: NIH Grant R01 AG077380

Title: Deep learning to detect postural instability in early, untreated Parkinson's disease

Authors: *D. ENGEL, P. I. BURGOS, P. CARLSON-KUHTA, F. B. HORAK, J. G. NUTT, M. MANCINI;
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Abstract: Postural instability constitutes a common motor symptom of Parkinson’s disease (PD). While there is evidence that postural instability may already be present pre-clinically, it is often associated with later stages of the disease. This is because current clinical or instrumented assessments may be insensitive to subtle changes and can only detect postural instability when clinically apparent. Hence, this study aims at providing a sensitive objective measure of postural instability that is easy to obtain and might facilitate earlier clinical detection. We assessed postural sway in 40 untreated, newly diagnosed individuals with PD (age: [52-78] 68 ± 7; Hoehn & Yahr scale: [1-3] 1.9 ± 0.4; MDS-UPDRS Part III Motor Score: [15-54] 31 ± 11; MDS-UPDRS Part III Postural Instability Rating: [0-3] 0.4 ± 0.7) and 72 healthy controls (HC, age: [46-83] 68 ± 8) while they were standing quietly for 30 s on a firm surface with their eyes open and their feet together. We recorded their medio-lateral (m-l) body motion with a single accelerometer placed on the Lumbar spine. Acceleration data was transformed into time-frequency-spectrograms (frequency range: 0-6 Hz) using wavelet decomposition. Each resulting spectrogram was then converted into a greyscale image and labelled according to group before being fed into a custom-built convolutional neural network for classification. 70 % of the labelled spectrogram images were used to train the network to distinguish between PD and HC. The remaining 30 % of samples were used for evaluation. We trained 25 independent models, each using data from different participants for training and evaluation in equally sized groups. A paired Receiver Operating Characteristics (ROC) analysis based on traditional measures of postural sway obtained from our data resulted in poor discrimination between groups (sway area: AUC = 0.52; m-l sway amplitude: AUC = 0.58; m-l frequency dispersion: AUC = 0.62). In contrast, our deep learning models trained on the frequency spectrograms reached a classification performance on the respective evaluation data with an average accuracy of 94.0 % along with excellent sensitivity and specificity (ROC-AUC = 0.97 ± 0.06). Our deep learning approach suggests a distinct feature in the frequency content of postural sway during quiet stance that may distinguish individuals with early, untreated PD from healthy controls. Given the simple nature of our recordings and the excellent classification performance, this method bears great potential to help clinicians in their assessment of postural impairments in early stages of PD.

Disclosures: D. Engel: None. **P.I. Burgos:** None. **P. Carlson-Kuhta:** None. **F.B. Horak:** A. Employment/Salary (full or part-time):; APDM Precision Motion, Clario. **J.G. Nutt:** None. **M. Mancini:** F. Consulting Fees (e.g., advisory boards); APDM Precision Motion, MJFF.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.24/I34

Topic: E.06. Posture and Gait

Support: R01 AG077380

Title: Digital gait biomarkers in newly diagnosed Parkinson's disease

Authors: *P. CARLSON-KUHTA[1], V. ARCOBELLI[2], D. ENGEL[1], P. I. BURGOS[1], V. V. SHAH[1], F. B. HORAK[1,3], M. MANCINI[1];
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Abstract: Background. Parkinson's disease (PD) is a neurodegenerative disorder identified by several key motor symptoms, that include bradykinesia, tremor, rigidity, and postural instability. Identification of objective measures for Parkinson’s disease early in the disease is crucial for tracking disease progression and developing effective interventions that can be initiated early to maximize potential benefits. Here we used machine learning to identify the best gait digital biomarkers to differentiate people newly diagnosed with Parkinson’s disease, and not yet taking anti-parkinsonian medication, from age-matched healthy controls (HC). Methods. We recruited 27 people with PD (age: [52-78] 69.1 ± 6.4 years; disease duration: [0.04-2.67] 0.92 ± 0.73 years; MDS-UPDRS-III total score: [15-46] 26.2 ± 7.8) and 16 age-matched healthy controls (age: [46-79] 66.2 ± 9.8 years). Participants completed 1) 2-minute walk test (2MWT), 2) 2-minute walk test with a cognitive dual task (2MWT with DT), and 3) 6-minute walk test, fast speed, while wearing seven OPAL inertial sensors (APDM Precision Motion, Clario, Portland). We extracted 24 gait measures using APDM Mobility Lab Software and the dataset was split 70% for training and 30% for testing. We evaluated the performance of five different machine-learning models: Random Forest, Support Vector Classifier, XGBoost, Gradient Boost Classifier, and KNeighborsClassifier. These models were optimized through a Grid Search CV approach, utilizing a 5-fold cross-validation (CV) to refine the hyperparameters. Models were evaluated on metrics like mean CV accuracy and ROC AUC for comprehensive assessment. We used SHAP (SHapley Additive exPlanations) to understand how different features influence the model’s predictions. Results. In a comparative analysis of the different walking conditions, the Random Forest algorithm outperformed achieving a mean CV accuracy of 0.85 and ROC AUC of 0.90, based solely on the 2MWT with DT, compared with results of 2MWT with no DT, that had CV accuracy of 0.81 and ROC AUC of 0.82. SHAP value analysis highlighted the most influential

features: mean coronal range of motion of the trunk, transverse range of motion, and gait speed. Conclusions. The 2MWT with DT results are in line with previous publications indicating that adding a DT is useful in discriminating HC and early PD. Machine learning methods can provide insights into determining the most appropriate gait biomarkers to track changes early in Parkinson's disease. One limitation is number of subjects, but we are continuing data collection. We will follow these participants for three years to further examine best measures to use longitudinally.

Disclosures: P. Carlson-Kuhta: None. **V. Arcobelli:** None. **D. Engel:** None. **P.I. Burgos:** None. **V.V. Shah:** A. Employment/Salary (full or part-time):; APDM Precision Motion, Clario. **F.B. Horak:** A. Employment/Salary (full or part-time):; APDM Precision Motion, Clario. **M. Mancini:** F. Consulting Fees (e.g., advisory boards); APDM Precision Motion, Clario, Michael J Fox Foundation.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.25/I35

Topic: E.06. Posture and Gait

Support: The Royal Society International Exchange Award

Title: Closed-loop paired brain and neuromuscular electrical stimulation system for enhancing corticospinal excitability of hand muscles in healthy adults

Authors: *M. TAYLOR[1], M. MILOSEVIC[2], N. JENKINSON[1], S.-Y. CHIOU[3];
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Abstract: Paired neuromuscular electrical simulation (NMES) and intermittent theta burst stimulation (iTBS) has shown to increase corticospinal excitability of a relaxed forearm muscle and the facilitatory effect was superior to NMES alone. However, it remains unclear whether the same facilitation can be observed in an active muscle. This study's aim was to investigate the effect of closed-loop paired iTBS and NMES triggered by EMG activity of the abductor pollicis brevis (APB), versus NMES alone, on corticospinal excitability of the APB. We hypothesized corticospinal excitability of the APB will increase to a greater extent after paired iTBS and NMES, compared with NMES alone. A screening session of iTBS alone was conducted to all participants and those who showed increased peak-to-peak amplitudes of motor evoked potentials (MEP) of APB, elicited by transcranial magnetic stimulation over the primary motor cortex, after the stimuli, were invited back to continue after 7 days. Nineteen young adults (22±2.1 years, 8 males) underwent the following two sessions in a random order, 7 days apart: 1) iTBS paired with NMES (iTBS+NMES), and 2) sham iTBS paired with NMES

(iTBSsham+NMES). iTBS intensity was set at 80% of active motor threshold. NMES frequency was set at 50Hz. Participants contracted the APB to 10% of maximal voluntary contraction to initiate the paired stimuli, which lasted ~192s. During stimulation, the participant held a peg in a relaxed state. MEP amplitudes of APB were assessed before, immediately after, and 10, 20, and 30 minutes after the paired stimuli. Results showed MEP amplitudes of the APB increased by 66% from the baseline immediately after the iTBS+NMES (66.4±74.1%; Z=-3.363, p=0.004) and the facilitatory effects last up to 30 minutes (by 65.2%, 52.4%, and 51.4% at 10, 20, and 30 minutes after; all $p<0.001$). The sham condition caused an increase in MEP amplitudes by 39% immediately after the intervention (38.9±48.1%; Z=-3.018, p=0.012), and the effect did not last. Our results revealed closed-loop paired iTBS with NMES increased the corticospinal excitability of the APB. We suggest paired iTBS and NMES may be used to facilitate the corticospinal excitability for enhanced efficacy of a subsequent intervention for hand function in clinical populations.

Disclosures: M. Taylor: None. **M. Milosevic:** None. **N. Jenkinson:** None. **S. Chiou:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.26/I36

Topic: E.06. Posture and Gait

Support: CMAR Pump-priming fund

Title: Vestibular control of postural adjustments in young and older adults

Authors: *S.-Y. CHIOU[1], L. FOULGER[2], J.-S. BLOUIN[3];
[1]Univ. of Birmingham, Birmingham, United Kingdom; [2]The Univ. of British Columbia, Vancouver, BC, Canada; [3]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Older adults exhibit balance deficits and experience falls. Age-related changes in the descending motor pathways may be contributing factors of such deficits. While it is evident that vestibular function declines with age, the specific age-related changes in its control during postural adjustments to counterbalance perturbations induced by voluntary movements of the upper extremities remain unknown. Here we examined the vestibular control during a self-initiated unilateral shoulder abduction task using continuous electrical vestibular stimulation (EVS) (bandwidth: 4.5-10.5 Hz) in 20 young (mean [SD] = 23 ± 4 years; 9 male) and 20 older adults (77 ± 4 years; 10 males). Participants were standing still on a force plate, with feet shoulder-width apart and eyes closed, while receiving the EVS. They were instructed to perform the task when ready, after a soft auditory cue (80dB, 500Hz), for a minimum of 80 times; breaks were given when needed to avoid fatigue. To compare vestibular control during standing and during preparation of the task, EVS and ground reaction force (GRF) signals were analysed in a 200ms window prior to the auditory cue (quiet standing) and the onset of the GRF (task

preparation). Anticipatory postural adjustments (APAs) associated with the task were quantified using the area of vertical torque prior to the initiation of the arm movement. The relationship between the EVS and GRF was estimated from the time window of the quiet standing and the task preparation using coherence and gain. Older participants exhibited smaller APAs (5.8 ± 12.6 Nm*ms) compared with young participants (15.8 ± 16.1 Nm*ms; $p<0.001$) prior to the initiation of the arm, indicating an age-related change in postural control. Coherence was reduced during task preparation (young: 0.038 ± 0.017; older: 0.045 ± 0.025) compared to quiet standing in both groups (young: 0.027 ± 0.020; older: 0.035 ± 0.025). There was no difference in gain or magnitudes of the GRF between quiet standing and task preparation. Our results suggest that a decrease in vestibular control of postural adjustments might contribute to the initiation of an upper-limb task, and that this control mechanism remained, despite impaired anticipatory postural response, with ageing.

Disclosures: S. Chiou: None. **L. Foulger:** None. **J. Blouin:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.27/I37

Topic: E.06. Posture and Gait

Support: International Spinal Research Trust Solomons Award
Academy of Medical Sciences Springboard Award

Title: Changes in spatial distribution of trunk muscle activation during forward reaching in individuals with subacute motor incomplete spinal cord injury

Authors: *J. A. KEARNEY[1], H. V. CABRAL[2], H. CHOUDHURY[3], S.-Y. CHIOU[4];
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Abstract: Trunk motor control is an important aspect in rehabilitating key motor skills and regaining functional independence and quality of life for people with spinal cord injury (SCI). However, it remains unknown how individuals with SCI regain volitional control of the trunk and whether the severity of the injury influences the recovery of the trunk. Here we examined spatial distribution of activation of the lumbar erectors spinae (ES) and trunk angular displacement during forward reaching at two time points four weeks apart in patients with subacute (< 3 months post-injury) motor incomplete SCI (AIS C and D) using high-density surface electromyography and an inertial measurement unit. Seventeen participants with motor incomplete SCI (post-injury: 66 ± 33 days) completed a baseline and a 4-weeks assessment. All participants received standard in-patient rehabilitation during the 4-weeks interval. Results

showed no differences in global root-mean-square (RMS) amplitudes of ES activity, cranio-caudal barycentre, or trunk angular displacement between the baseline and 4-weeks assessment. However, subgroup analyses revealed that participants classified as AIS C (N = 7) at the baseline showed a cranial shift of cranio-caudal barycentre at 4-weeks (mean upwards shift = 1.7 [0.03 3.40] 95% CI), suggesting that participants with AIS C recruited more upper part of the ES when performing forward reaching during recovery. Conversely, participants classified as AIS D (N = 10) showed no change in the cranio-caudal barycentre after 4 weeks. AIS motor score realisation (scores based on an individual's room to improve) improved in both groups: AIS C showed a mean improvement of 20.0% [3.32 36.64] 95% CI, while AIS D improved 20.8% [0.58 40.94] 95% CI. Moreover, changes in trunk angular displacement did not differ between groups at baseline and 4-weeks. Our results demonstrated that changes in neuromuscular control of the trunk can be observed within 3 months post-injury in participants with AIS C - those with more severe injuries - suggesting a therapeutic window to implement activities that target enhanced recovery of trunk function. No change in neuromuscular control of the trunk in participants with AIS D could mean that the injury-induced change in the neuromuscular control of the trunk might happen earlier than the observational window of this study.

Disclosures: J.A. Kearney: None. **H.V. Cabral:** None. **H. Choudhury:** None. **S. Chiou:** None.

Poster

PSTR349: Posture and Gait: Aging, Injury, and Disease

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR349.28/I38

Topic: C.03. Parkinson's Disease

Support: NIH NINDS Grant R15NS087447-02

Title: Novel method to estimate the contributions of individual muscles to a person's tremor

Authors: N. HOWES[1], M. ALLEN[1], D. FARINA[3], ***S. CHARLES**[2];
[1]Mechanical Engin., [2]Mechanical Engin. and Neurosci., Brigham Young Univ., Provo, UT;
[3]Bioengineering, Imperial Col. London, London, United Kingdom

Abstract: Peripheral methods for suppressing hand tremor, like botulinum toxin injections, filtering orthoses, and electrical stimulation, show potential. However, we do not know where (which muscles or joints) to intervene most effectively because we do not know which muscles contribute most to an individual's tremor. Because tremor at the hand represents a convolution of tremorogenic activity from many muscles, determining which muscles contribute most to an individual's tremor is challenging. We have recently developed a method to quantitatively estimate the contribution of each muscle to an individual's tremor. This method relies on novel measures of coherence (frequency-dependent correlation). In a system with uncorrelated inputs, coherence attributes measured output power to each input. Yet, in a system with correlated inputs (as in tremorogenic muscle activity), existing coherence measures cannot distinguish between the

contributions of each input. To bridge this gap, we generalized existing concepts of coherence, defining two new coherence measures: component coherence and contribution coherence. Component coherence optimally decomposes output power into distinct components, each of which can be interpreted physically in terms of either power from a given input or cross power due to interference between a pair of inputs. Contribution coherence, which describes the portion of the output power that would be removed if the given input were removed, is calculated as the sum of all component coherence terms associated with the specified input. We have applied this novel method to surface sEMG from four major wrist muscles (inputs) and hand translation in three degrees of freedom (outputs) recorded from 14 subjects with Essential Tremor. Using component and contribution coherence, we analyzed segments exhibiting definitive tremor and high multiple coherence, and we computed the contribution from each muscle. Averaged across subjects, as well as in some individual subjects, we found statistically significant differences in the amount of contribution between some muscles. For example, in one subject, the flexor carpi radialis muscle had far more contribution than any other muscle, suggesting that—in this subject—tremor could be substantially reduced by targeting this muscle and sparing the other muscles. Averaged across subjects, we found that targeting wrist flexor or radial deviator pairs appears optimal for tremor suppression. Future research will expand this analysis to include all major superficial muscles of the upper limb.

Disclosures: N. Howes: None. **M. Allen:** None. **D. Farina:** None. **S. Charles:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.01/I39

Topic: E.09. Motor Neurons and Muscle

Title: Deciphering the neural mechanisms of physical training improving locomotor speed

Authors: *W. LIU[1,2], W. REN[1], N. N. GUAN[1], J. SONG[1];
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Abstract: Locomotor behaviors allow human and animal to interact with the environment. In vertebrates, spinal neural circuits are named the central pattern generator (CPG). These spinal circuits, owing to their modular organization, drive the sequential recruitment of motoneurons from slow to intermediate and then fast as speed increases. The spinal motor neurons (fast, intermediate, and slow motor neurons) receive and integrate both excitatory and inhibitory synaptic inputs respectively, thereby driving correspondent muscles to perform locomotion. Long-term exercise training can accelerate muscle contraction and increase locomotion speed. However, the neural mechanism behind this phenomenon remains unclear. In this study, we found that 4 weeks of physical training can significantly improve zebrafish swimming speed.

EMG shows aggregated burst firings in on-cycle muscle activity post-training, accelerating muscle contraction and enhancing swimming efficiency. Behavioral analysis indicates that after training, under the same swimming resistance, zebrafish use lower swimming frequencies dealing with low swimming resistance, and lower swimming amplitudes dealing with high swimming resistance, increasing locomotion potency. Electrophysiological results show that the intrinsic properties of motor neurons remain unchanged after training. However, we observed stronger inhibitory inputs to slow motor neurons alongside stable excitatory inputs, contributing to accelerated muscle contraction during swimming. We further found that stronger inhibitory inputs received by slow motor neurons after training are likely postsynaptic due to the increased glycine receptor expression anchored on the slow motor neurons.In conclusion, this study reveals that an upregulation of glycine receptors on slow motor neurons leads to increased inhibitory input to the slow motor neurons after training. Thus, burst firings in the on-cycle phase of muscle activity become aggregated with an earlier occurring and a prolonged mid-cycle phase, enhancing muscle contractility.

Disclosures: W. Liu: None. **W. Ren:** None. **N.N. Guan:** None. **J. Song:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.02/I40

Topic: E.09. Motor Neurons and Muscle

Support: NIA/NIH Grant R01AG067758
NIA/NIH Grant R01AG078129

Title: Weighted Cart Pull: A Method for Assessing Motor Function in Mouse Models and Its Application to Aging Studies

Authors: *S. N. AYYAGARI[1], P. J. MOORE[2], C. BRENNAN[2], Z. WILLIARD[2], N. R. KERR[2], J. A. VITERI[3], A. ROSHANI DASHTMIAN[2], F. B. DARVISHI[4], W. ARNOLD[5];
[1]Univ. of Missouri-Columbia, Columbia, MO; [2]Univ. of Missouri, Columbia, MO; [3]Physical Med. and Rehabil., Univ. of Missouri, Columbia, MO; [4]NextGen precision Hlth., Columbia, MO; [5]NextGen Precision Hlth., Univ. of Missouri, Columbia, Columbia, MO

Abstract: Sarcopenia, which involves age-related muscle weakness and atrophy, significantly reduces physical function and heightens mortality risk among older adults. Despite this, treatment options are scarce. While preclinical models typically use tests such as rotarod and grip strength to evaluate muscle strength and coordination, clinical research suggests that measurements of motor power might offer more relevant insights into the functional capabilities of older adults. Consequently, we aimed to develop a preclinical method for assessing motor power in mouse models and compare this new method with established behavioral motor

function tests. We placed 120cm ramp at a 7-degree angle, 18.7 cm off the ground. A resting chamber with food pellets was covered with a plastic board at the top of the ramp. A plastic toy track and support grip were taped to the center of the ramp. A cart was constructed with two sets of LEGO Wheels and two 2x8 LEGO Parts. Cotton Umbilical Tape was attached between the LEGOs and the mouse's tail. A plastic 100 mL beaker was secured to the wheelbase. Steel weights were added to create the "weighted cart".19 C57BL/6N mice (10 male, 9 female) underwent a training phase of weighted cart pull with 5g/g body weight. 10 mice were young (6 months) and 9 were old (24 months). The testing phase was 5-6 days after the training phase. Mice pulled 10g/g, 12g/g, 14 g/g body weight and so on till they could no longer pull the cart. Rotarod and all limb grip were performed one week after the weighted cart pull. Electrophysiology and muscle contractility were measured two weeks after max weight testing. A separate cohort of 4-5-month-old C57BL/6N mice (50% female) underwent repeated testing at baseline, day 4, and day 10 to assess test re-test reliability. Old mice pulled a significantly less max weight than young mice in both absolute (unpaired t test, p value = 0.0163) and normalized measures (unpaired t test, p value = <0.0001). Max pull was significantly correlated with absolute all limb grip (Pearson correlation, r = 0.6035, p = 0.0062). Rotarod and max pull had a Pearson correlation coefficient of r = 0.3336 (p = 0.1627). The test-retest cohort showed a coefficient of variation of 8.7% at day 4 and 10.5% at day 10. The weighted cart pull test is an effective tool for assessing motor function and detecting changes in overall muscle power during aging. It also correlates well with other established muscle behavior measures, such as all-limb grip strength. These characteristics suggest that the weighted cart pull test is both sensitive and reliable for evaluating comprehensive motor power, making it suitable for use in preclinical studies of aging and neurodegenerative diseases.

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Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.03/J1

Topic: E.09. Motor Neurons and Muscle

Support: Falk Medical Research Trust Catalyst Award

Title: Disruption of Neuregulin Signaling in Microglia Stops Disease Progression in ALS

Authors: J. LIU[1], D. TIU[1], J. A. LOEB[1], G. CORFAS[2], ***F. SONG**[1];
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Abstract: We previously identified multiple subtypes of motor neurons and inflammatory glial cells (microglia) from sporadic amyotrophic lateral sclerosis (ALS) patient spinal cords (1). We also have implicated that neuregulin1 (NRG1) (a glial growth factor) receptors are constitutively activated on microglia in both human ALS and the SOD1 G93A mouse model (2,3). Blocking NRG1 signaling with a potent, targeted antagonist slows disease onset and spread in mice (4). These findings raise the hypothesis that NRG1 is released from degenerating motor neurons to specifically activate surrounding microglia into a pathological phenotype, thus promoting disease spread and progression. Activation of microglia is a key pathological feature in ALS and other neurodegenerative diseases. However, the therapeutic potential of modulating pathological microglia activation is unexplored. In this study, we investigated the role of NRG1, a glial growth factor, in microglial-mediated neurodegeneration using a genetic model that selectively blocks NRG1 signaling on microglia by expressing an inducible dominant-negative NRG1 (erbB4) receptor in SOD1 G93A mice. We found that inhibiting the erbB4 receptor on microglia suppressed pathological microglial activation, and preserved synapses and motor neurons in the spinal cord, resulting in prolonged survival of most SOD1 mice for over 12 months compared to the control SOD1 mice (who died within 4-5 months). Our findings reveal how NRG1 signaling on microglia contributes to neurodegenerative disease progression and suggest that blocking NRG1 signaling is a promising therapeutic strategy for ALS. **References:** (1) Dachet, Liu, Ravits, Song. Predicting disease stage specific spinal motor neurons and glia in sporadic ALS patients. Neurobiol Dis. 2019. (2) Song, Chiang, Wang, Ravits, Loeb. Aberrant neuregulin 1 signaling in ALS. J Neuropathol Exp Neurol. 2012. (3) Song, Chiang, Ravits, Loeb. Activation of microglial neuregulin1 signaling in the corticospinal tracts of ALS patients with upper motor neuron signs. Amyotroph Lateral Scler Frontotemporal Degener. 2014. (4) Liu, Allender, Wang, Simpson, Loeb, Song. Slowing disease progression in the SOD1 mouse model of ALS by blocking neuregulin-induced microglial activation. Neurobiol. Dis. 2018.

Disclosures: J. liu: None. **D. Tiu:** None. **J.A. Loeb:** None. **G. Corfas:** None. **F. Song:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.04/J2

Topic: E.09. Motor Neurons and Muscle

Title: Voluntary running exercise improves synaptic degeneration in the anterior cingulate cortex of knee osteoarthritis mice, improving pain and anxiety disorders.

Authors: *R. MIYAKE[1], M. YAMANAKA[2], M. YUKI[3], N. NISHIO[4], T. UENO[5], T. NAKATSUKA[6], W. TANIGUCHI[7], H. YAMADA[8];
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Univ. of Hlth. Sci., Osaka, Japan; [7]Dept. of Orthopaedic Surgery, Wakayama Med. Univ., Wakayama, Japan; [8]Wakayama Med. Univ., Wakayama/Wakayama, Japan

Abstract: Osteoarthritis of the knee (knee OA) is a musculoskeletal disorder that causes chronic pain and can also lead to emotional disorders such as anxiety. Exercise therapy is known to be effective for this condition. The anterior cingulate cortex (ACC) is one of the cerebral cortical areas that governs emotions. When electrically stimulated, it induces a form of synaptic strengthening known as Long-Term Potentiation (LTP). Although LTP in the ACC is considered a model for pain mechanisms driven by anxiety, there have been no reports on its connection with chronic pain caused by knee OA or its relation to exercise therapy. In our study, we prepared brain slices from mice with knee OA and from those that underwent voluntary exercise with knee OA. We examined the induction and maintenance of LTP in the ACC using the whole-cell patch-clamp method. Additionally, we used microinjection into the ACC to study pain avoidance behaviors and anxiety-like behaviors in mice with knee OA. While LTP was induced in the sham group, it was not induced in the knee OA group. Therefore, when HCN channel blockers (ZD7288) and protein kinase Mζ inhibitors (ZIP) were infused into the bath, the amplitude of evoked excitatory postsynaptic currents (eEPSCs) decreased. In the knee OA group, there was a significant increase in pain avoidance and anxiety-like behaviors. Conversely, microinjections of ZD7288 and ZIP into the ACC of the knee OA group significantly improved these behaviors. Furthermore, in knee OA mice that underwent voluntary exercise, pain avoidance and anxiety-like behaviors significantly decreased. Surprisingly, LTP, which was not expected to be induced, was also triggered. In knee OA mice, LTP had already been induced, and microinjections of ZD7288 and ZIP into the ACC improved pain avoidance and anxiety-like behaviors. This suggests that knee OA causes synaptic plasticity changes in the ACC, which may be involved in chronic pain and emotional disorders such as anxiety. Furthermore, these synaptic plasticity changes could potentially be ameliorated by exercise therapy.

Disclosures: R. Miyake: None. **M. Yamanaka:** None. **M. Yuki:** None. **N. Nishio:** None. **T. Ueno:** None. **T. Nakatsuka:** None. **W. Taniguchi:** None. **H. Yamada:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.05/J3

Topic: E.09. Motor Neurons and Muscle

Title: Corticospinal Tract Monosynaptic Neuronal Partners Includes Spinal Motor Neurons Before and After Motor Cortex Stroke

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[4]Univ. of Texas Hlth. Sci. Center, San Antonio, San Antonio, TX; [5]Neurol., Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Stroke leaves many patients with significant motor impairment. Sprouting of the contralesional corticospinal tract (cCST) into the injured spinal hemicord is associated with improved motor recovery after unilateral primary motor cortex stroke. In adult mice, most corticospinal neurons project to spinal interneurons, and few synapse directly on alpha motor neurons. We investigated the distribution and cellular type of cervical spinal neurons that are reinnervated by the cCST after unilateral M1 stroke in both hemicords. Utilizing anterograde transsynaptic AAV injection in multiple transgenic mouse lines, serial two-photon tomography (STPT) and light sheet fluorescent microscopy (LSFM) of whole cervical cords, and automated registration and quantification via SpinalTRAQ, we hypothesized that post-stroke cCST synapse distribution correlates directly with the locations of reinnervated spinal neurons and that they are stereotypic motor subtypes. We induced a photothrombotic motor cortex stroke or performed sham surgery (n=6 per group) in 8-10 week old male and female Ai9 or Sun1-sfGFP mice and administered a transsynaptic anterograde AAV1-cre injection into the contralesional motor cortex 6 weeks after injury. Cervical cords were processed through SpinalTRAQ, a custom end to end pipeline that utilizes either STPT or LSFM, machine learning based feature characterization, volumetric registration to a custom 3D reference volume, and automatic quantification of features within atlas regions. We characterized the anatomical location of spinal neurons with monosynaptic connections to the cCST pre and post-stroke including extensive characterization of direct synaptic innervation of motor neurons of lamina 9. Reinnervation of phenotypically appropriate spinal interneurons, and previously overlooked direct spinal motor neuron connections, by the contralesional motor cortex may contribute to functional recovery after motor cortex stroke.

Disclosures: M. Kenwood: None. **D. Betz:** None. **P. Rhoton:** None. **D.M. Ramirez:** None. **M.P. Goldberg:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.06/J4

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant NINDS K99126576

Title: Synaptic responses of regenerated motoneurons to injury spared reflex circuits

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Abstract: Axotomy of a peripheral nerve results in the permanent deletion of IA synaptic boutons onto homonymous motoneurons. Consequently, the stretch-evoked monosynaptic reflex is abolished which contributes to persistent motor deficits known to occur following injury. Deficits are also noted in stretch reflexes initiated by uninjured synergist muscles, and the reason(s) for the failure of heteronymous reflexes to compensate remain unsettled. In this study, we transected the medial gastrocnemius (MG) nerve followed by an immediate repair in adult rats. Approximately one year following the initial injury, we conducted intracellular recordings from spinal MG motoneurons *in vivo* using sharp electrodes and recorded stretch-evoked synaptic potentials in response to MG stretch (homonymous) or stretch of the lateral gastrocnemius/soleus (LGS) muscle group (heteronymous). We found, as predicted based on published work from our lab, that the homonymous connectivity was severely impaired following regeneration with the majority of motoneurons failing to respond to stretch and those that did respond produced diminished amplitudes. However, the heteronymous inputs remained functional and were capable of eliciting synaptic potentials with functional connectivity and synaptic efficacy comparable to controls These data suggest that non-injured IA are not permanently impaired following nerve injury and that these connections maintain the ability to encode propriosensory information. This means that coordinated limb movement might be restored by therapy directed at uninjured heteronymous synapses. Furthermore, these data suggest that axotomy of the motor axon alone is not sufficient for permanent presynaptic deletion, i.e., that both disconnection of the pre- and postsynaptic element from their peripheral target is what most likely drives the permanent synaptic deletion.

Disclosures: T.M. Rotterman: None. **P. Nardelli:** None. **T.C. Cope:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.07/J5

Topic: E.09. Motor Neurons and Muscle

Support: JSPS KAKENHI Grant Number 23K16655

Title: Effectiveness of combined both mirror therapy and contralateral controlled functional electrical stimulation therapy for stroke patient with upper limb motor paralysis

Authors: *K. AOKI[1,3], K. UCHIBORI[3,4], M. WATANABE[3,5], T. WATABE[3,4], T. MIYATA[5], A. YOSHIKAWA[2];
[1]Showa Univ., Yokohama-shi, Kanagawa, Japan; [2]Div. of Hlth. Sci. Educ., Showa Univ., Yokohama/Kanagawa, Japan; [3]Div. of Occup. Therapy, Dept. of Rehabilitation, Sch. of Nursing and Rehabil. Sciences, Showa Univ., Yokohama, Japan; [4]Dept. of Rehabil. Center, Showa Univ. Fujigaoka Rehabil. Hosp., Yokohama, Japan; [5]Dept. of Rehabil. Division, Showa Univ. Koto Toyosu Hosp., Tokyo, Japan

Abstract: Patients with severe upper limb motor paralysis after stroke significantly reduces patients' social participation and quality of life, so that acute rehabilitation therapy for these patients are important. Rehabilitative therapy for upper limb motor paralysis with patients is performing, e.g. mirror therapy or, contralateral controlled functional electrical stimulation (CCFES) therapy. However, Severe upper limb motor paralysis does not improve adequately. Although sufficient therapeutic mechanisms have not yet been elucidated, we considered that the simultaneous therapy of these two methods might facilitate the improvement of motor paralysis because of the differences in neurophysiological mechanisms both these therapies. Therefore, the aim of this study was to develop a combined rehabilitation strategy combining mirror therapy and CCFES therapy for patients with severe upper limb motor paralysis. In this case report, we report on the benefits of combined therapy. Patient is 50s old man with subcortical haemorrhage on CT who underwent craniotomy. Two weeks after, he was transferred to rehabilitation hospital. Before start of the combination therapy, the Fugl-Meyer Assessment for Upper Extremity (FMA-UE) was 17 points. Combined therapy was conducted for 12 weeks (20 min/once, 5 times/week) At the end of combined therapy, FMA-UE, Modified Ashworth Scale (MAS) and Motor Activity Log (MAL) were 52 points, 1, AOU:3.6, QOM:3.9, respectively. In this case, combined treatment with mirror therapy and CCFES resulted in an improvement in left hand motor function, suggesting the usefulness of combined therapy. combined treatment with mirror therapy and CCFES Neurotransphysiological mechanisms are thought to lead to activation of neural networks involved in movement, such as activation of the primary motor system, balance between cerebral hemispheres, which improves functional disability. In the future, EEG measurements will be performed to provide neuroscientific support for the efficacy of the therapy.

Disclosures: K. Aoki: None. **K. Uchibori:** None. **M. Watanabe:** None. **T. Watabe:** None. **T. Miyata:** None. **A. Yoshikawa:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.08/J6

Topic: E.09. Motor Neurons and Muscle

Support: K12HD093427

Title: The impact of post-stroke motor overflow modulation on unilateral and bilateral asymmetric force production

Authors: *R. JIN[1,2], P. TOMKO[1,2], S. RAMANI[2], D. A. CUNNINGHAM[1,2,3];
[1]Case Western Reserve Univ., Cleveland, OH; [2]MetroHealth Ctr. for Rehabil. Res., Cleveland, OH; [3]Cleveland Functional Electrical Stimulation Ctr., Cleveland, OH

Abstract: Bimanual activities are commonplace during activities of daily living, involving dynamic load balance between homologous motor cortices. Coordinating asymmetry between limbs necessitates the modulation of motor overflow between hemispheres, where motor overflow refers to the unintentional activation of one hemisphere during the intended activation of the other. Following a stroke, bilateral motor performance is compromised, and it remains unclear whether the deficits are specific to the ipsilesional hemisphere or are influenced by the contralesional hemisphere. Transcranial magnetic stimulation (TMS) is a tool that can non-invasively induce cortical-level population neuronal discharge at the motor cortex. TMS-induced motor-evoked potential (MEP) can be recorded from the participants' muscle electromyography (EMG) while conducting unimanual and bimanual isometric contractions to help understand how motor overflow is modulated under different load conditions. We hypothesize that impaired modulation of motor overflow from the contralesional to the ipsilesional hemisphere may influence overall bimanual performance post-stroke. Thirteen stroke participants were enrolled. All outcomes were measured during the isometric grip force, where the paretic hand (test hand) force was at 0 (rest; unilateral condition), 5, or 30% of its maximal voluntary contraction (MVC) (bilateral condition), while the non-paretic hand (conditioning hand) was at 0 (rest), 10, 30, or 70% of its MVC. Under each condition, EMG was recorded from the flexor carpi radialis, and 10 TMS stimulations were delivered for each condition. We found that on the group level, the ipsilesional hemisphere can modulate the motor overflow during the bilateral tasks (i.e., reduced MEP amplitudes) compared to unilateral conditions across all force levels. However, those individuals with poor motor overflow modulation (i.e., increased MEP amplitudes in the test hemisphere) also demonstrated poorer force stability while maintaining 5% and 30% MVC of the paretic hand. These results differ from our earlier study involving able-bodied subjects, where poor bimanual performance was associated with over-modulation of motor overflow (decreased MEP amplitudes). The current results, therefore, suggest a relationship between over-modulation and inadequate modulation of motor overflow and its impact on bilateral performance. Post-stroke, individuals exhibiting inadequate modulation of motor overflow from the contralesional to the ipsilesional hemisphere may encounter more pronounced bilateral deficits.

Disclosures: R. Jin: None. **P. Tomko:** None. **S. Ramani:** None. **D.A. Cunningham:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.09/J7

Topic: E.09. Motor Neurons and Muscle

Support: National Research, Development and Innovation Fund, Hungary, GINOP 2.3.3-15-2016-0003222
National Research, Development and Innovation Fund, Hungary,TKP2021-EGA-35

Title: Comparison of investigator-release and automata-release mechanisms when applying Pendulum Test to assess quadriceps muscle tone in able bodied persons

Authors: P. MAYER[1], N. ZENTAI[1], A. BODOR[1,2], L. BOTZHEIM[2,1,3], ***J. LACZKO**[2,4,5,1]; [1]Univ. of Pecs, Pecs, Hungary; [2]Wigner Res. Ctr. for Physics, Budapest, Hungary; [3]Rehabil. Clin., Semmelweis Univ., Budapest, Hungary; [4]Fac. of Information Technol. and Bionics, Pazmany Peter Catholic Univ., Budapest, Hungary; [5]Shirley Ryan AbilityLab, Chicago, IL

Abstract: The spasticity of the quadriceps muscle is objectively measured by the Wartenberg pendulum test (WPD). In the WPD usually an examiner holds and then unexpectedly releases the foot of the participant who is sitting semi-supine or laying (supine) on a bed with the thigh settled on the bed, and the knee fully extended at the edge of the bed. Spinal cord injured people may not perceive the moment of foot release, for them it is an unexpected event. Though, able-bodied test participants interfere with the examiner and before the examiner releases the foot, they expect it from the examiner's actions and hand movements. This can influence the movement pattern of the swinging leg. To prevent this, we investigated the influence of an automata leg releasing mechanism on muscle tone measured by WPD in healthy persons whom muscle tone is often compared to the spastic muscle tone of patients with neurologic disorders. Methods: 15 healthy adults (9 males, 6 female, age: 23.2 ± 3.2 yr.) were examined. Markers were placed on their anatomical landmarks: greater trochanter of the femur, lateral epicondyle of the femur, upper end of the fibula, and lateral malleolus of the fibula. A Zebris 3D ultrasound-based motion analysis system was used to record marker positions (50Hz sampling rate) during the WPD. The test was completed in investigator-release and automata-release mode, in which the examiner released the leg or an automata release mechanism was applied. Time course of knee angle, the number of swings of the leg, and the relaxation index was computed from marker coordinates. Paired *t* tests with the significance level of .05 were applied in comparison of the data obtained applying the 2 releasing modes. Results: a) Comparing the number of swings in investigator- versus automata-release mode, no significant differences were found. Although, when automata-release was used, the number of swings was lower in the dominant than in the non-dominant leg in both body positions, while in investigator-release mode this happened only in laying position. b) In automata-release mode the relaxation index was significantly lower in supine than in semi-supine position in both legs, while in investigator-release mode this could not be observed in either leg. Conclusion: The effect of leg-dominance and body position on the quadriceps muscle tone can be discerned using the WPD with an automatic leg releasing mechanism even when the application of investigator-release mode doesn’t show such effect. This observation should be considered when the spasticity of the quadriceps muscle of people with neural injury, as spinal cord injury or stroke, is compared to muscle tone of healthy people.

Disclosures: P. Mayer: None. **N. Zentai:** None. **A. Bodor:** None. **L. Botzheim:** None. **J. Laczko:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.10/J8

Topic: E.09. Motor Neurons and Muscle

Title: The Clinical, Genetic, and Epigenetic Basis of Extrapyramidal Symptoms in Schizophrenia: Implications for AI-Based Solutions

Authors: *M. SHARMA;
Smart Healthcare, IIT-AIIMS Jodhpur, Jodhpur, India

Abstract: Extrapyramidal symptoms (EPS) are adverse reactions experienced by patients with schizophrenia due to the use of antipsychotic medications. These symptoms can severely impact a patient's well-being, posing significant challenges in their treatment journey. This meta-analysis explores the latest findings from clinical, genetic, and epigenetic research on EPS, shedding light on how AI-based solutions can revolutionize patient care in schizophrenia.
Through a systematic review of studies gathered from reputable databases like PubMed and PsycINFO, this meta-analysis focuses on understanding the interplay of clinical, genetic, and epigenetic factors contributing to EPS in schizophrenia. Previous research has highlighted the role of genetic variations in dopamine receptor genes, such as DRD2 and DRD3, as well as epigenetic modifications like DNA methylation and histone acetylation, in influencing individuals' susceptibility to EPS.
AI-based methodologies offer promising avenues for predicting, detecting, and managing EPS in schizophrenia. Machine learning algorithms, for instance, can analyse complex datasets comprising genetic, clinical, and epigenetic to identify patterns and predict an individual's risk of developing EPS. Additionally, wearable devices equipped with sensors can continuously monitor patients' motor function and symptom severity, allowing for timely intervention and adjustment of treatment plans.
In conclusion, the integration of clinical, genetic, and epigenetic research findings with AI-based solutions has the potential to significantly improve the management of EPS in schizophrenia. By harnessing the power of AI, clinicians can personalize treatment strategies, optimize patient care, and ultimately enhance the well-being of individuals living with schizophrenia.

Disclosures: M. Sharma: None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.11/J9

Topic: E.09. Motor Neurons and Muscle

Title: Characterizing Differences Between Schwann Cells and Motor Neurons Differentiated from Healthy and ALS Patient-Derived hiPSCs

Authors: *D. ARORA, M. DAU, G. MCCABE, V. TRUONG, P. WALSH;
Anatomic Inc., Minneapolis, MN

Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by the progressive loss of motor neurons, leading to muscle weakness and eventual paralysis. Modeling ALS using human induced pluripotent stem cell (hiPSC)-derived motor neurons and Schwann cells offers a promising avenue to study disease mechanisms and develop potential treatments. We have previously shown that human induced pluripotent stem cells (hiPSCs) can be rapidly differentiated into highly pure populations of motor neurons and Schwann cell precursors (SCPs) using small molecules and growth factors - without the need for the overexpression of transcription factors. Here, we show that motor neurons and SCPs can be generated from both a healthy and ALS TDP43 patient (ND50007) hiPSC lines at high purity, and look at both expression and functional differences. Motor neurons expressed key markers ISLT1, HB9, TDP-43, CHAT and SCPs were S100β+, SOX10+, MITF- via immunocytochemistry. Comparative expression to analogous tissues via qPCR confirmed the identity of the cell types. To study disease phenotypes, the variable expression of cryptic exon genes in both healthy and ALS motor neurons were measured in untreated and sodium arsenite treated cultures. We found that HDGFL2, ACTL6B were upregulated while PFKP, STMN2, ELAVL3, RCAN1 were downregulated in ALS phenotypes, matching previously published studies from the field. Using the Axion Maestro multiwell microelectrode array (MEA), both healthy and ND50007 motor neurons were plated alone and in co-culture with SCPs. We show that healthy and ALS motor neurons have differences in baseline functional activity and co-cultures with SCPs have an accelerated and increased firing rate. We also plan to look at functional differences with SCPs derived from the TDP43 mutant line. By recapitulating key aspects of ALS pathology in vitro, such models enable researchers to investigate the underlying molecular and cellular mechanisms driving disease progression.

Disclosures: D. Arora: A. Employment/Salary (full or part-time):; Anatomic Incorporated. **M. Dau:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. **G. McCabe:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. **V. Truong:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated. **P. Walsh:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.12/J10

Topic: E.09. Motor Neurons and Muscle

Support: R21 NS130367-01

Title: Alterations in muscle synergies during isometric upper limb movements at different contraction levels in chronic stroke patients.

Authors: *S. BAE[1,2], S. CHANDRA[3], W. Z. RYMER[4], ***S. BAE**[5];
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Abstract: Stroke severely disrupts intermuscular coordination in the upper limb, leading to abnormal co-activation that hinders movement and reduces the quality of life for patients. Muscle synergy analysis, a technique that extracts underlying patterns from EMG data, reveals how a set of coordinated muscle activation patterns are combined to achieve various movements. Stroke survivors often exhibit increased pathological coupling, or co-activation, between elbow and shoulder muscles in the affected upper limb. Our study aimed to examine how muscle synergy patterns change with varying contraction levels during isometric upper limb movements. Three chronic stroke survivors with moderate motor impairment participated in this study. Force/torque and EMG data were collected from chronic stroke survivors using the KAIST Upper Limb Synergy Investigation System (KULSIS) during eight isometric tasks (elbow flexion/extension, wrist pronation/supination, flexion/extension, adduction/abduction of shoulder). KULSIS measures force/torque exerted on the wrist and captures sEMG signals from key upper limb muscles (Biceps, Triceps, Pronator Teres, Brachialis, Brachioradialis, Medial Deltoid, Anterior Deltoid, and Pectoralis Major). Each task included a maximum voluntary contraction (MVC) trial followed by trials at 20% and 40% MVC, with participants aiming for a steady force for 10 seconds with visual feedback. For precision, the subject was seated in a Biodex chair, their forearm was immobilized with custom orthopedic fiberglass material. Raw EMG signals from eight upper limb muscles underwent multi-stage filtering and rectification to extract the envelope. Following normalization, Non-negative Matrix Factorization (NMF) analysis identified three or four unique muscle synergies for each contraction level with minimal reconstruction error (<0.01%). Previous studies suggest that individuals without impairments typically have around five synergies in their upper limbs, while stroke survivors often have only four, indicating reduced movement complexity. Our results align with these findings but reveal that contrary to the expected proportional relationship, activation coefficients, and synergy vectors vary significantly across tasks and muscles, depending on the level of MVC. Specifically, there is coupling between upper-arm and shoulder muscles, as well as between chest and forearm muscles. These findings highlight the need for comprehensive models that account for task-specific and muscle-dependent variations.

Disclosures: S. Bae: None. **S. Chandra:** None. **W.Z. Rymer:** None. **S. Bae:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.13/J11

Topic: E.09. Motor Neurons and Muscle

Title: Cortical suppression increases force drift and reduces motor unit variability in the sensorimotor system

Authors: *Y. R. ESCALANTE, J. KHIM, Y. LEI;
Texas A&M Univ., College Station, TX

Abstract: Cortical suppression increases force drift and reduces motor unit variability in the sensorimotor system*Yori Escalante, James Khim, Yuming LeiProgram of Motor Neuroscience, Department of Kinesiology & Sport ManagementTexas A&M University, College Station, TX, 77843.*Visual feedback is an important tool used to update the internal dynamics of our sensorimotor system. In established research, the removal of visual feedback for performance during a sustained isometric contraction often results in a force drift, where force production either increases or decreases compared to the movement goal. This suggests that the sensorimotor system is contingent upon less reliable feedback systems, such as proprioception and somatosensation, for updating the end effector. In our experiment, we recruited healthy young adults (n = 72) and manipulated visual feedback during an isometric force tracking task to reveal its crucial role in the interplay between sensory input, motor planning, and action execution. Additionally, we used an advanced electromyography sensory and low-frequency (1-Hz) online inhibitory repetitive transcranial magnetic stimulation to examine the impact of the primary motor cortex, somatosensory cortex, and supplementary motor area on performance and motor unit activity during the task. Our preliminary findings have suggested that the removal of visual feedback reduces force output in all groups. Furthermore, although the primary motor cortex exhibits a consistent significant decrease ($p<0.05$) in force output throughout the period of visual feedback removal, the supplementary motor area demonstrates an initial decline in force output followed by a recovery period. Additionally, there were no differences between our sham stimulation group and stimulation groups regarding force output variability. In contrast, when analyzing our high-density surface electromyography data, we found significantly higher variability ($p<0.05$) in motor unit firing rate for our sham group compared to our stimulation groups. This may suggest that the presence of internal planning variability within the system, which is highly noticeable when critical planning areas, such as our regions of interest, are not suppressed. To our knowledge, we are the first to investigate how the inhibition of different cortical areas disrupts updating downstream components of the motor pathway and task performance in a force-drift paradigm. Our examination of behavior and motor unit activity in response to varying dynamics can help elevate the field by revealing how motoneurons react to internal and external changes in their respective environments.

Disclosures: Y.R. Escalante: None. **J. Khim:** None. **Y. Lei:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.14/J12

Topic: E.09. Motor Neurons and Muscle

Support: NIH grant R01 NS 053606

Title: A system for identifying upper-extremity movements that lead to the preferential use of the corticospinal tract post-stroke

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Abstract: Repeated voluntary movements are critical for inducing neural rewiring and renormalization following a stroke. However, movements that can cause maladaptive neural reorganization have been overlooked. To achieve true behavioral restitution, it is necessary to induce the preferential use of the ipsilesional hemisphere and corticospinal tract. Our team strives to develop a monitoring and feedback system that identifies upper-extremity movements that induce the preferential use of the ipsilesional neural networks, by matching the movement with its corresponding cortical activity. The first step is to develop a real-time arm movement tracking device with high accuracy, high fidelity, and low cost. A flexible arm sleeve is used for easy donning and doffing. The sleeve embeds multiple inertia measurement units (IMUs) for each segment of the upper extremity to estimate the angles of anatomical joints, including the shoulder (3 degrees of freedom), elbow (1 DOF), supinator/pronator (1 DOF), and wrist (2 DOF). Deep learning is employed to guarantee high accuracy and robustness. We use synthetic movement data from the Unity game engine to simulate a wide variety of arm movements. A Unity-based human anthropometric model allows simulation of realistic IMU data depending on movements. The long short-term memory neural network is trained with features of the synthetic data that are irrelative of arm segment dimension and mass, and IMU placement. We found that once trained, the network produces accuracies (variance for account) beyond 95% of angle estimation about the major axes of joints, including the shoulder, elbow and supinator/pronator, in the synthetic database. We will apply this trained neural network to estimate joint angles using signals of the IMUs embedded in the arm sleeve in real-time.

Disclosures: L. Oshea: None. **K. Kinnerk:** None. **A. Ramirez:** None. **S. Lee:** None. **D. Kim:** Other; Kim owns EpicWide, LLC. **J.L. Patton:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.15/J13

Topic: E.09. Motor Neurons and Muscle

Support: NIH T32 HD101395

Title: The monoaminergic relationship between motoneuron neuromodulation and descending nociceptive inhibition.

Authors: *A. BENGTSSON[1], S. T. JENZ[1,2], J. A. BEAUCHAMP[1,5], E. CHIEN[1], A. ACOSTA[1], C. HECKMAN[1,2,3,6], J. P. DEWALD[1,3,4];
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Abstract: Chronic pain conditions are often associated with weakness and impaired endogenous descending nociceptive inhibition (DNI) mediated by reticulospinal monoaminergic neurotransmitters (serotonin, norepinephrine). This phenomenon ("pain inhibiting pain") can be quantified by comparing a noxious testing stimulus before and after a noxious conditioning stimulus such as submerging the foot in cold water (cold pressor test [CPT]). When this mechanism is intact, the monoaminergic signal activates inhibitory interneurons at the dorsal horn, which in turn dampens or blocks subsequent noxious input from the periphery. This process attenuates nociceptive signal intensity reaching the cortex where they can be readily measured via electroencephalography (EEG). Serotonin and norepinephrine are also strong neuromodulators vital to the prolongation and amplification of spinal motoneuron (MN) firing. Previous studies have validated the use of high-density surface electromyography (HDsEMG) arrays to measure MN neuromodulation, allowing for the estimation of monoaminergic drive from brainstem nuclei to αMNs. Our central hypothesis is that a positive relationship exists between DNI and MN neuromodulation, based on the overlap in neurotransmitters, brainstem circuitry, and clinical concurrence of weakness and impaired DNI. This project is conducted in young healthy controls and will be followed by participants with chronic pain conditions. MN firing patterns of the vastus lateralis are measured via discharge rate hysteresis (ΔF) during isometric knee extension contractions, using HDsEMG. Surface EEG is utilized to measure the cortical response to noxious electrical stimuli at the 5th digit (frequency = 1 Hz; duration = 200 s; intensity = sensory threshold x20), followed by submersion of the contralateral foot in 8°C water for two minutes (CPT). Both HDsEMG and EEG measurements are repeated immediately after. In order to compare results from EEG and HDsEMG, we standardized the measurements by subtracting the pre- from the post-CPT values and dividing by their sum. Negative values for the EEG index indicate improved DNI, whereas positive values for the HDsEMG index indicate an increase in ΔF. Our preliminary data thus far demonstrates improved DNI (n = 2, male; EEG index = -0.423, -0.234) and an increase in ΔF (n = 1, male; HDsEMG index = 0.087) following the CPT. Data collection is ongoing and will allow for a more robust assessment of the

relationship between these monoaminergic processes. Uncovering the relationships between DNI and MN neuromodulation will add to our basic understanding of the interplay between pain processing and motor function.

Disclosures: A. Bengtsson: None. **S.T. Jenz:** None. **J.A. Beauchamp:** None. **E. Chien:** None. **A. Acosta:** None. **C. Heckman:** None. **J.P. Dewald:** None.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.16/J14

Topic: E.09. Motor Neurons and Muscle

Title: Optimized protocol for intra-operative motor mapping

Authors: *C. KAPELLER, K. MAYR, C. GUGER;
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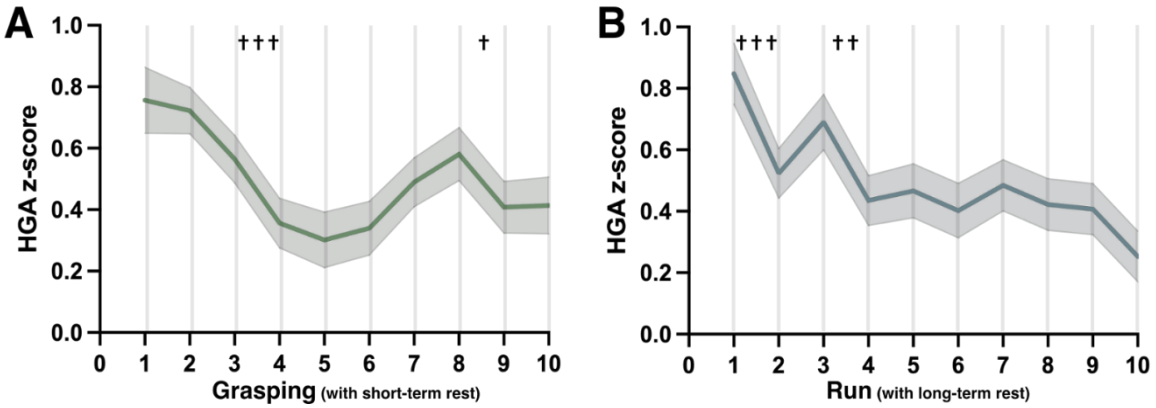
Abstract: Glioma or epilepsy resection often requires awake craniotomies with intraoperative mapping. This procedure poses challenges for both surgical teams and patients, underscoring the importance of minimizing mapping time. Utilizing electrocorticography (ECoG) for passive mapping shows promise in streamlining intraoperative efforts through direct electrical stimulation. This study aims to optimize mapping protocols for hand movement, focusing on duration and localization accuracy. 3 patients underwent awake craniotomy at Asahikawa Medical University and Kindai University. Patients were maintained at a bispectral index above 90 to ensure wakefulness during mapping. Data were acquired at 1200 Hz. Each session comprised 10 runs, each of 250s, with a 12s rest phase (baseline) followed by a 12s grasping period containing ten grasping movements. High-gamma activity (HGA, 60-170Hz) was recorded from ECoG locations on the pre- and postcentral gyrus. Locations displaying significant grasping-related HGA, with stronger responses during early trials or runs, were "attenuated." Of the 37 electrodes on the sensorimotor cortex, 16 exhibited significant HGA during short-term grasping. 3 locations demonstrated significant attenuation after three runs, with 1 location showing attenuation after the first 3 trials within a run. The short-term and long-term attenuation effects over repetitions grasping and runs are depicted in Figure 1 A and B, respectively. The attenuation effect of short-term repeated movements during intraoperative monitoring is initially modest. However, with increased repetitions, the number of attenuated locations rises. Consequently, minimizing overall mapping time is paramount, rather than reducing the number of tasks per block. For statistical analysis, 20 grasping trials (2 runs of 10 movements) or 48 s is recommended. Alternatively, a mapping protocol involving a third run or 30 trials (72 s) may enhance data robustness. These preliminary findings, though based on a limited cohort, require further investigation, particularly in epilepsy patients.



Disclosures: C. Kapeller: A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **K. Mayr:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **C. Guger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); g.tec medical engineering GmbH.

Poster

PSTR350: Motor Neurons in Exercise, Injury, and Disease With a Focus on Human and Non-Primate Mammal Models

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR350.17/J15

Topic: E.09. Motor Neurons and Muscle

Title: An in vitro human induced pluripotent stem cell-derived platform to model cortico-motor neuron circuitry

Authors: M. AUROUSSEAU[1], P. ZHOU[2], N. BUTELET[2], D. LESSARD[2], W. W. POON[2], ***A. M. MAROOF**[3,2];
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Abstract: The cortico-motor circuit consists of cortical glutamatergic “upper” motor neurons (UMN) that project onto and form synapses with spinal cord cholinergic “lower” motor neurons (LMN), which then synapse onto skeletal muscle, resulting in motor function and movement. This circuit becomes dysfunctional and progressively degenerates in diseases such as amyotrophic lateral sclerosis (ALS). Here, we describe the generation of human induced pluripotent stem cell (iPSC)-derived UMN and LMN. Each neuronal population expresses the appropriate molecular markers at the gene and protein levels and exhibit typical neuronal electrophysiological properties when assessed using multi electrode arrays. The development of these cryopreserved, ready-to-use neurons enabled assembly of UMN/LMN circuits within microfluidics-based devices. Cultured UMN extended axons through microfluidic channels and formed synaptic contacts onto LMN in adjoining chambers. Similarly, cultured LMN extended

axons and formed synaptic contacts onto human skeletal muscle cultured in adjoining chambers. Functional calcium transients were detected in circuits containing both UMN and LMN. This *in vitro*-based microphysiological system (MPS) recapitulates salient features of the cortico-motor circuit in which we observed phenotypic differences in ALS patient-derived UMN and LMN when compared to non-disease controls. Taken together, our cryopreserved human iPSC-derived neurons can be combined to form a MPS that emulates human cortico-motor circuitry and translates into a novel *in vitro* platform for drug discovery.

Disclosures: M. Aurousseau: None. **P. Zhou:** None. **N. Butelet:** None. **D. Lessard:** None. **W.W. Poon:** None. **A.M. Maroof:** None.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.01/J16

Topic: E.09. Motor Neurons and Muscle

Support: Canadian Institute of Health Research Project Grant (PJT 180556)

Title: Spinal dI3 neuron circuits are involved in skilled and corrective locomotor behaviours

Authors: *S. CHIASSON, E. KHAN, A. M. LALIBERTE, T. V. BUI;
Biol., Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Many spinal neurons integrate sensory input to adapt a wide array of movements. Prior research has shown that spinal dorsal interneuron 3 (dI3) neurons receive cutaneous and proprioceptive sensory input and that they project to motor circuits, most notably through excitation of motoneurons. We sought to better delineate the spinal circuits within which dI3 neurons operated. To reach this objective, we tested motor performance of transgenic mice where dI3s could be chemogenetically silenced by the DREADD receptor, hM4Di. Chemogenetic inhibition of dI3s was concomitant with drug treatments that putatively inhibited recurrent motoneuron excitation of central targets such as Renshaw cells. These mice were then tested on three behavioural tasks. For performance related to fine motor control, balance, and coordination, mice were tested on a vibrating balance beam and horizontal ladder walking task. In both ladder and beam tasks, mice demonstrated an up to three-fold increase in the incidence of foot falls after dI3 inhibition. A similar effect was observed after mecamylamine administration, an antagonist of Renshaw cell excitation, where foot falls doubled on average. Interestingly, ladder and beam tasks performed after a combined treatment that silenced both dI3s and Renshaw cell excitation, did not appear to have a compounding effect; the increase in foot falls remained two to three-folds. Additionally, mice were also tested on a treadmill apparatus wherein the hindlimb paw was either mechanically or electrically perturbed to attempt to trigger the stumble corrective reaction. The effects of dI3 inhibition and mecamylamine administration were less pronounced for this task, wherein step height and step cycle duration demonstrated

only subtle changes compared to control sessions. Overall, our findings support the hypothesis that dI3s are involved in sensory information processing and integration, wherein proprioceptive and cutaneous signals may be used to modulate the activation of muscles during locomotion. While there remains much to be understood about dI3 spinal circuits, it appears that a lack of dI3 signaling may inhibit skilled locomotor behaviours. Our experiments begin to identify the spinal circuits within which dI3s operate to shape motor activity.

Disclosures: S. Chiasson: None. **E. Khan:** None. **A.M. Laliberte:** None. **T.V. Bui:** None.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.02/J17

Topic: E.09. Motor Neurons and Muscle

Support: Canadian Institute of Health Research Project Grant (PJT 180556)

Title: Machine learning of EMG signals during locomotion

Authors: *E. KHAN, A. M. LALIBERTE, S. CHIASSON, T. V. BUI;
Biol., Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Automated detection of locomotor activity from electromyogram (EMG) signals is useful for data analysis and closed-loop stimulation applications. We sought to develop a computational model of locomotor EMG signals using machine learning that would be able to recognize electrical noise and stimulus artifacts and calculate locomotion properties. Our current model analyzes in-vivo, pre-recorded, EMG signals of limb muscles during mouse locomotion. EMG recordings were sectioned into small time-slices (10ms). Machine learning was used to train a model to recognize each time-slice as either baseline signal, high-amplitude electrical noise, stimulation artifacts or locomotor EMG bursts. The model was trained using over 7000, 10-ms, time-slices from a training dataset obtained across 6 locomoting mice. Each time-slice was characterized using over 30 features including time integral, the first derivative and the frequency of the signal crossing its mean value. This trained model was then evaluated using a separate testing dataset. The sensitivity of our model to correctly detect baseline signal and high-amplitude noise is over 90% and its sensitivity to correctly detect stimulus artifacts and muscle activity is approximately 70 %. The detection of noise and stimulus artifacts allows us to automate the removal of these types of signals or to perform stimulus-triggered analyses. The processed locomotor EMG signal can then be used to calculate the characteristics of locomotor step-cycles . This machine learning model of locomotor EMG signals facilitates the analysis of EMG recordings and can potentially be used to implement real-time, closed-loop, stimulation for applications requiring rapid detection of locomotor activity.

Disclosures: E. Khan: None. **A.M. Laliberte:** None. **S. Chiasson:** None. **T.V. Bui:** None.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.03/J18

Topic: E.09. Motor Neurons and Muscle

Support: Simons-Emory International Consortium on Motor Control
Emory University Synergy Award

Title: EMUsort and LITMUS: the Enhanced Motor Unit sorter and robust benchmarking of motor unit sorters

Authors: *S. O'CONNELL[1,3], J. A. MICHAELS[4], R. WANG[6], M. VENKATESH[3], N. ARESH[3], T. OYA[4], A. PRUSZYNSKI[5], S. J. SOBER[2], C. PANDARINATH[7];
[2]Biol., [1]Emory Univ., Atlanta, GA; [3]Biomed. Engin., Georgia Inst. of Technol., Atlanta, GA; [5]Physiol. and Pharmacol., [4]Western Univ., London, ON, Canada; [6]Johns Hopkins Univ., Baltimore, MD; [7]Biomed. Engin., Emory Univ. and GA Tech., Decatur, GA

Abstract: Tracking the influence of descending neural drive onto muscle fibers during force production is a key focus of motor neuroscience. Each motor neuron and the muscle fibers it innervates constitute a single *motor unit*. Recent advances in intramuscular multielectrode arrays enable high-quality multichannel recordings of motor unit action potentials (MUAPs) for the first time, but the methods to classify and sort these MUAPs are generally unreliable because existing spike-sorting methods were optimized for cortical neuron characteristics. In addition, literature and infrastructure for evaluating MUAP sorter performance is critically lacking. We therefore present 1) the Enhanced Motor Unit sorter (EMUsort), a Kilosort-based MUAP sorter, and 2) the Leaderboard Interface for Testing Motor Unit Sorters (LITMUS), a public leaderboard for benchmarking MUAP sorter performance. With EMUsort, we attempted to address some of the unique challenges encountered with MUAP data, including: 1) higher waveform diversity versus cortical data, 2) potentially large time delays across electrodes due to propagation along fibers, and 3) high degree of MUAP overlaps during high-force behaviors. First, the initialization of templates (waveform patterns used for "matching" to produce spike times) is improved via K-means clustering on all spike examples, followed by a controlled choice of the least correlated waveform shapes for initial matching prior to full template learning. In addition, the dimensionalities for clustering (principal components) and for low-rank representation of templates (singular values) are both increased. To address the second challenge, the time delays between MUAP peaks are minimized by performing an optimal shift of each channel to produce the highest total cross-channel correlation. Using the LITMUS benchmarking methods to quantify metrics such as precision, recall, accuracy, and fraction of units identified, we found EMUsort achieved 92.2% mean accuracy across 10 ground truth MUAP clusters, whereas Kilosort3 scored 85.1%. In regions of high overlap, EMUsort scored 83.0% (69.9% for Kilosort3), indicating greater stability across the range of MUAP activity levels. With LITMUS, users will be able to download ground truth simulated datasets (based on rat, human, or monkey

data), run their own sorter, upload their results for evaluation, and publish their ranked results. EMUsort is currently being compared to the recently-released Kilosort4, and will incorporate the new algorithms if performance is improved. In sum, EMUsort and LITMUS provide urgently needed tools for sorting of intramuscular MUAP datasets and for sorter evaluation.

Disclosures: S. O'Connell: None. **J.A. Michaels:** None. **R. Wang:** None. **M. Venkatesh:** None. **N. Aresh:** None. **T. Oya:** None. **A. Pruszynski:** None. **S.J. Sober:** None. **C. Pandarinath:** None.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.04/J19

Topic: E.09. Motor Neurons and Muscle

Support: NIH R01 NS047357
NIH U24 NS126936
NIH 1R01NS099375-01A1
NIH T32NS096050

Title: Tools for high resolution electromyography in neonatal mice.

Authors: *W. MCCALLUM[1,2,3], O. MISTRETTA[4], K. A. THOMAS[5], M. WILLIAMS[3], S. J. SOBER[3], F. J. ALVAREZ[2];
[1]Emory Univ. Neurosci. PhD Program, Atlanta, GA; [2]Cell Biol., [3]Biol., Emory Univ., Atlanta, GA; [4]Cell Biol., Emory Univ., Acworth, GA; [5]Emory Univ., Atlanta, GA

Abstract: The functional organization of spinal circuits during the postnatal maturation of the motor system is highly understudied, in large part due to the lack of methods for the interrogation of motor function *in vivo*. To study motor output during postnatal development, we have developed minimally invasive, implantable high-density microelectrode arrays (MEAs) for flexible and high-resolution electromyography (EMG) recordings of single motor units in awake behaving p7 to p12 mouse pups. These devices (a modification of the Myomatrix arrays described in Chung *et al.* 2023) allow simultaneous recordings from multiple muscles to collect high-quality bulk EMG recordings that can be leveraged for analysis of single-unit motoneuron firing patterns. Here, we are applying this technology to interrogate the postnatal development of motor units across joints in the hindlimb of mice. For this purpose, we evoke limb rhythmic stepping by administration of a subcutaneous injection of L-DOPA in neonate mice, resulting in a behavior in which the animals reliably display a wide-range of the intra- and inter-limb coordination patterns controlled by spinal cord premotor circuits, while allowing separation of limb coordination from weight-bearing and postural adjustments that occur during over-ground locomotion. L-DOPA induced air-stepping in neonatal mice also enables the study of the maturation of neonatal motor unit properties and their control from spinal circuits during

dynamic behaviors and across multiple muscles simultaneously. Using this behavior in combination with novel EMG device designs, we can now interrogate motor units and motor circuits at a level of resolution higher than ever previously available, allowing for examination of single motor unit spiking patterns and their maturation during the postnatal period of motor development.

Disclosures: W. McCallum: None. **O. Mistretta:** None. **K.A. Thomas:** None. **M. Williams:** None. **S.J. Sober:** None. **F.J. Alvarez:** None.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.05/J21

Topic: E.09. Motor Neurons and Muscle

Support: JSPS KAKENHI Grant Number 22KK0139

Title: The Sternohyoid Muscle Function on Breathing and Swallowing in Rats

Authors: *C.-R. PAN, T. CHOTIRUNGSAN, N. DEWA, Y. TSUTSUI, J. MAGARA, T. TSUJIMURA, M. INOUE;
Niigata Univ., Niigata, Japan

Abstract: Motivation: The sternohyoid muscle (SH) is an infrahyoid muscle located bilaterally along with the trachea. Although its main function is to depress the hyoid bone, the role in breathing and swallowing is not clear. In this study, we aim to investigate the involvement of SH in swallowing reflex, especially how its activity is affected under conditions of airway stenosis and fixed muscle length.**Methods:** Anesthetized rats were used in three-part experiment. In the first part, electromyograms (EMGs) were used to evaluate the activities of undetached SH, thyrohyoid muscle (TH), anterior belly of digastric muscle (Dig), and diaphragm (Dia) during swallowing with airway stenosis. In the end of the first part, SH was detached at its insertion in order to fix the muscle length because the myotatic reflex may cause SH contraction during swallowing. In the second part, SH contraction was measured by a force transducer and EMGs. The third part tried to confirm neuron activation by motoneuron recordings.**Results:** SH activity coincided with inspiration and swallowing which showed coordination with Dig and TH. During airway stenosis, respiratory activity was intensified in all muscles, especially in the extra-thoracic muscles. However, swallowing activity was only facilitated in Dig but not in TH or SH. Swallowing activity was not observed in the SH when it was fixed, although inspiratory activity persisted. Motoneurons in the detached SH were not activated during swallowing.**Conclusion**: During the inspiration, SH is slightly activated. The effect of airway stenosis on the respiratory function may vary between muscles of the upper airway and Dia. The swallowing CPG does not have predominant control over the swallowing activity in SH; alternatively, SH could be activated by the myotatic reflex.

Disclosures: C. Pan: None. **T. Chotirungsan:** None. **N. Dewa:** None. **Y. Tsutsui:** None. **J. Magara:** None. **T. Tsujimura:** None. **M. Inoue:** None.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.06/

Topic: E.09. Motor Neurons and Muscle

Title: Effect of Isoflurane on reflex motor pathways activated by 10kHz vs. single pulse spinal cord stimulation on PDN rats

Authors: *D. LEE[1], K. LEE[2], Z. B. KAGAN[3];
[1]Nevro, Redwood City, CA; [2]Res., Nevro Corp, San Diego, CA; [3]Nevro Corp., Lake Oswego, OR

Abstract: Painful diabetic neuropathy (PDN) is a significant complication affecting approximately 20% of individuals with diabetes mellitus. A recent randomized controlled clinical trial demonstrated the potential efficacy of 10kHz spinal cord stimulation (SCS) as a promising therapy for PDN, showing both pain reduction and potential neurological improvements (Petersen et al., 2023). High-frequency (10kHz) spinal cord stimulation (SCS) is a well-established and expanding neuromodulatory technique for treating chronic pain, as well as activating motor circuits to restore motor function. We reported 10kHzSCS and single pulse stimulation activated different muscles. We aimed to study the effect of Isoflurane (ISO) concentrations on the activation of reflex motor pathways by 10 kHz SCS versus single pulses in the spinal circuits.SCS was applied via a micro-sized, in-line quadripolar electrode array positioned epidurally over the L5-L6 dorsal spinal segments (innervating the left hind paw). We applied a paired pulse protocol of 10kHz SCS (symmetric biphasic; pulse width: 20us; duty-cycled: 3ms ON with 5s OFF), as well as single pulse/low-frequency SCS (symmetric biphasic; pulse width: 200us; frequency: 0.2Hz) with delays ranging from 20ms to 500ms. Both strategies were applied at different times on the same two stimulating contacts (configuration: bipole) on diabetic pain development (on day 14 after STZ injection). Needle electromyograms (EMG) were taken of compound muscle action potentials (CMAP) from the hindlimb thigh (biceps femoris) and back muscle. We investigated the effect of Isoflurane concentration, ranging from 0.8% to 3%, on CMAP amplitudes of paired pulse responses on two different muscles by 10kHz SCS and single pulse SCS strategies, in terms of absolute peak-to-peak (ptp) amplitude and ratio between first (R1) and second (R2) responses from paired pulses.We observed that higher concentrations (>1.5%) decreased the CMAP ptp for both muscles and reached a steady state after >60 minutes. The R2/R1 ratio of thigh muscle activated by 10kHz SCS changed over 40% with low (1.5%~1%) ISO concentrations, while the back muscle activated by paired single pulses showed an insignificant change (<10%). This implies that 10kHzSCS may activate neural circuits and inhibitory spinal/brain networks influenced by ISO.

Disclosures: D. Lee: A. Employment/Salary (full or part-time):; Nevro. **K. Lee:** A. Employment/Salary (full or part-time):; Nevro. **Z.B. Kagan:** A. Employment/Salary (full or part-time):; Nevro.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.07/J22

Topic: E.09. Motor Neurons and Muscle

Support: NIA/NIH 1R01AG067758
NIA/NIH R01AG078129
Missouri Spinal Cord Injury/Disease Research Program (SCIDRP)

Title: Profiling age-related loss of motor function: corticospinal excitability, a major contributor to weakness?

Authors: *F. B. DARVISHI[1], A. ROSHANI DASHTMIAN[2], S. AYYAGARI[2], P. MOORE[2], C. BRENNAN[2], N. KERR[2], B. CLARK[3], W. ARNOLD[4];
[1]NextGen precision Hlth., Columbia, MO; [2]NextGen precision Hlth. Univ. of Missouri, Columbia, MO; [3]Ohio Univ., Athens, OH; [4]NextGen Precision Hlth., Univ. of Missouri, Columbia, Columbia, MO

Abstract: Impaired physical function is an important consequence of age leading loss of independence, and increased risk of mortality and morbidity. Coordinated function of the central nervous system (CNS), peripheral nervous system (PNS), and skeletal muscle is required for muscle contraction to allow performance of day-to-day tasks. As such, failure across these systems may contribute to loss of physical function. Historically, sarcopenia, pathological age-related loss of muscle size and strength, has been viewed primarily as a muscle failure, but growing evidence suggest neurological contributions. The goal of this project was to apply assessments of the CNS, PNS, and skeletal muscle in the C57BL/6 mouse model of aging to understand the pathophysiological drivers of motor dysfunction. A total of 32 old C57BL/6 mice (24-26 months) and 19 young controls (3-4 months) underwent assessments of motor function (grip, rotarod, and weighted cart pull test), assessments of corticospinal excitability (motor evoked potential following cervical spinal cord stimulation, cMEP), motor unit number estimation (MUNE), and muscle excitability (CMAP), as well as muscle contractile function. Electrophysiological and physiological assessments were performed in the hindlimb plantarflexor muscles. Motor function assessment demonstrated a 30% reduction in grip (strength), 23% reduction in rotarod (coordination) time, and 29% reduction in maximum power (weighted cart pull test) ($p<0.0001$ for all three tests). Electrophysiological studies demonstrated a 32% decline in the cMEP ($p<0.0001$), 33% decrease in motor unit number ($p<0.0001$) respectively), and 18% reduction in CMAP ($p=0.0001$). Muscle contractility revealed a 29% decrease ($p<0.0001$). When we profiled the associations between function and physiological

decline in the aged mice, MEP showed the strongest association with motor function (grip strength and weight pulling test, $r=0.64$, $p<0.0001$, and $r=0.49$, $p=0.005$ respectively). These comprehensive evaluations allowed us to capture a significant decline in muscle strength, coordination, and power as well as physiological decline across the CNS, PNS, and muscle systems in aged mice. Strong association between cMEP and motor function suggests that corticospinal excitability may be a major determinant of motor function in aged mice. These findings underscore the potential of modulating CNS excitability as a promising strategy to counteract age-related declines in physical function and sarcopenia.

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Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.08/J23

Topic: E.09. Motor Neurons and Muscle

Support: NSF DBI 2015317 as part of the NSF/CIHR/DFG/FRQ/UKRI-MRC Next Generation Networks for Neuroscience Program.

Title: Communication, coordination, and control in neuromechanical systems: Synergistic interactions

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Abstract: Brains are embodied. Many fundamental questions remain unanswered: How is neural information encoded and communicated? How does the system correct for environmental perturbations? How do passive biomechanics affect the neuronal control of behavior? This leads to the foundational question: How do nervous systems control and execute interactions with the environment? Our international Network of interdisciplinary research groups (IRGs), which incorporates modelers, engineers, and experimentalists, is exploring the Communication, Coordination, and Control of Neuromechanical Systems (C^3NS).
As an animal's length-scale and behavioral time-scale change, the relative importance of forms of energy also changes. We have created a framework that quantifies the changes in these forms of energy and enables us to predict control and responses to perturbations. Thus, we have chosen

to study three different groups of animals that exemplify these different dominant energy regimes.
IRG1 is developing the framework as well as tools and technologies that are broadly applicable to neuromechanical modeling. IRG2, by focusing on legged locomotion in adult *Drosophila melanogaster*, investigates the effect of scale and speed in a system dominated by viscous forces. IRG3, by focusing on feeding in the soft-bodied marine mollusk *Aplysia californica*, investigates the effect of changing size in a system dominated by elastic forces. IRG4, by focusing on legged locomotion in mice, rats, cats, and dogs, investigates the effects of changing size and joint parameters on dynamic control in systems in which inertial forces increasingly dominate.

Disclosures: R.D. Quinn: None. **H.J. Chiel:** None. **N.S. Szczecinski:** None. **V.A. Webster-Wood:** None. **A.J. Hunt:** None. **A. Bueschges:** None. **E. Andrada:** None. **M.C. Tresch:** None. **G.P. Sutton:** None.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.09/J24

Topic: E.09. Motor Neurons and Muscle

Support: NIH F31 NS124347
NSF CRCNS 1515140
NIH U01 EB021921

Title: Modular motor control and perturbation analyzed using stochastic dynamic operators

Authors: *T. S. SMITH[1], T. D. SANGER[2], S. F. GISZTER[1];
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Abstract: How the spinal cord translates various motor tasks into muscle activations is uncertain. In the motor modularity model of movement, dynamic ‘building blocks’ are combined to compactly construct most motor commands. We define a motor ‘module’ as a neural element evoking stereotyped motor activity, extracted from kinetic or biological features (e.g., synergist muscle EMG). In the spinal frog, modularity can be studied using the hindlimb-to-hindlimb wiping reflex as a behavior composed of three motor modules. The spinal capacity to execute this motor activity can be challenged by varied perturbations, including intraspinal microstimulation (ISMS). During wiping, the spinal cord must control when modules are recruited and how modules coordinate the motor pools. Historical work within the spinal bullfrog model has used spike-triggered averaging to identify neurons, active during modular pulses, with significant post-spike facilitations to multiple muscles, consistent with synergy. Exogenously activating the spinal cord with ISMS drives motor activity, and combinations of ISMS-evoked responses resemble spinal reflexes, suggesting a common facilitation. Consistent with historical

data, in most cases, ISMS evokes a single pulse of motor activity, corresponding to a single factor in both force trajectory and muscle activations. Our data indicate that these ISMS responses emerge from limited recruitment of interneurons and associated single motor units within and across motor pools. By triggering ISMS before, during, and after the execution of the wiping reflex, we have challenged the spinal motor activity. In most instances, the ISMS-induced motor activity resolves quickly and is modularly 'inserted' into the ongoing motor plan. However, ISMS specifically during the onset of reflexive motor activity causes differential effects conditional on the prior and induced vector limb heading evoked by each stimulus: Comparable vectors superimpose while opposing vector headings result in execution of only a single response. Some interneurons and single motor units are selectively facilitated by ISMS or wipe, and others are recruited by both stimuli. We have adapted the Stochastic Dynamic Operator (SDO) framework to describe the spike-triggered changes in signal dynamics. SDOs can be functionally clustered to identify interneurons and motor units commonly contributing to observed or latent factors (e.g., modules), and gain-scheduled SDOs can reconstruct stochastic signals, including EMG. Our results point towards a neuromuscular definition of motor modularity in the spinal frog motor repertoire and its responses to perturbations.

Disclosures: T.S. Smith: None. **T.D. Sanger:** None. **S.F. Giszter:** None.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.10/J25

Topic: E.09. Motor Neurons and Muscle

Support: SK524945

Title: Effect of short vs long-term ovariectomy on Pcm reflex activity in Wistar rats

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Abstract: We have been described that the multifuncional Pcm reflex activity evoked by clitoris stimulation is compound of phasic on-off and tonic on-off responses (the last called afterdischarges). Its characteristics depends on the estrus cycle phase chose for recording. Thus, during late proestrus and early estrus (were estradiol levels are high) afterdischarges are present, however during diestrus are absent. This effect can be related to the fluctuations of estradiol levels during the estrus cycle. That means that the low levels of estradiol during the diestrus can be the reason why there are not reflex afterdischarges. This was corroborated by us when recordings was done after ovariectomy and estradiol was injected. The afterdischarges appeared after 5min after injection.Recordings in short term (3-7 weeks) ovariectomized rats showed the

same effect. In the present work we explored if long term (1-2 years) ovariectomy mantains the same effect. Methods. The Pcm reflex activity was recorded in Wistar rats previously ovariectomized at 90 days old. They were grouped in so called “short term” ovariectomy (3-7 weeks) and “long term” ovariectomy (1-2 years). The reflex Pcm activity was recorded during mechanical clitoris stimulation in animals under urethane anesthesia (dosis). Injections of estradiol at (dosis) were applied. Results. In the “short term” group, the reflex activity was compound of tonic on responses without afterdischarges, independently if the recording was done 3, 4, 5, 6 or 7 weeks post ovariectomy. After estradiol injection, intense afterdischarges with longer duration appeared. In the “long term” group, the reflex activity was compound of tonic on and off responses with afterdischarges independently if the recording was done 1 or 2 years post ovariectomy. Injection of estradiol produced the appearance of more afterdischarges with longer duration. Discussion. There is a “long term” compensatory effect related with the sensory circuit provoked by the presence of long term low estradiol circulating levels.

Disclosures: O. Lara-García: None. **M.K. Serrano:** None. **M.A. Lara Garcia:** None. **P. Pacheco:** None.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.11/J26

Topic: E.09. Motor Neurons and Muscle

Support: JSPS KAKENHI (Grant Number 22H00587)
National Institute of Information and Communications Technology (NICT) (No.22801)
JST Moonshot R&D Grant (JPMJMS2011)

Title: Knee extension generated by spinal root stimulation at cauda equina with chronically implantable electrodes on a Non-Human Primate.

Authors: *T. YAN[1], Y. LIU[1], L. LIU[1], T. KAIJU[2], M. HIRATA[3];
[1]Grad. Sch. of Medicine, Osaka Univ., Osaka, Japan; [2]Natl. Inst. of Information and Communications Technol., Suita, ; [3]Osaka Univ. Clin. Neuroeng, Suita, Japan

Abstract: A spinal cord damage interrupts the communication between the motor area of cortex and the peripheral nerves controlling lower limb muscles, leading to paralysis. Approaches based on surface/intramuscular stimulation and epidural/subdural spinal cord stimulation were tested to enable natural control of stand and walk functions. In this study, we designed and implanted a helix with 12 electrodes on the ventral spinal roots of right lumbar 5 segment at cauda equina in a single Japanese macaque (macaca fuscata) monkey. Electrical stimuli with different frequencies, amplitudes and pulse widths were used to produce movement contraction patterns of muscles relevant to the knee extension. These implantable epineural electrodes were well

tolerated in the intraspinal space for more than 2 months. Our interface selectively and reliably activated quadriceps (rectus femoris), generating knee extension, and sustained contraction forces. This preliminary study demonstrated that cauda equina approach and spinal root (ventral side) stimulation can be a new sight in functional electrical stimulation aiming at lower limb movements of stand and walk for neuroscience research and future clinical applications.

Disclosures: T. Yan: None. **Y. Liu:** None. **L. Liu:** None. **T. Kaiju:** None. **M. Hirata:** None.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.12/J27

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant R00 NS119787

Title: Modeling the flexibility of cortical control of motor units

Authors: *C. SURMEIER[1], E. A. AMEMATSRO[2], N. J. MARSHALL[2], M. M. CHURCHLAND[2], J. I. GLASER[1];
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Abstract: Alpha motor neurons within the spinal cord orchestrate muscle contraction by selectively innervating distinct muscle fibers, forming the fundamental motor control unit known as a "motor unit" (MU). For nearly a century, researchers have explored the sequential recruitment of MUs, with prevailing hypotheses suggesting a size-based sequential engagement paradigm. However, this theoretical framework primarily derives from experiments involving static or gradually changing forces - recent results, using experiments with a much wider range of force profiles, have shown otherwise. To explain motor unit activity across a wide range of movement conditions, multiple degrees of freedom were needed. Still, a large question remains - what underlies this flexibility of MU control? Is it driven by the cortex across wide ranges of movement? To gain a more comprehensive understanding of the adaptable control signals influencing motor units, we developed a machine learning model that incorporates relevant biological constraints and recapitulates experimental data from simultaneous Neuropixel recordings in the primary motor cortex (M1) and MU recordings of arm muscles in macaques performing diverse force production profiles. Our model framework predicts MUs from M1 neurons through a low-dimensional bottleneck, in order to test how many degrees of freedom within M1 were beneficial for predicting MU activity. More specifically, a linear encoding scheme translates M1 activity into a latent dimension of variable size, which is then decoded through a monotonic neural network to predict MU activity. We found that models with a one-dimensional bottleneck were not able to accurately predict all motor units, particularly those selectively active during high-frequency oscillatory conditions. A notable enhancement in predictive accuracy was observed upon augmenting the latent dimension, as evidenced by a

substantial increase in R2 value on a held-out validation set. As opposed to classic theories suggesting a single common drive of cortical activity to MUs, our results strongly suggest cortical flexibility over motor unit control.

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Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.13/J28

Topic: E.09. Motor Neurons and Muscle

Support: NSF CBET-1932192
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NSF STC-EBICS Grant CBET-0939511
Alzheimer's Disease Association grant 2019-AARG-NTF-644507

Title: Nerves prompt the secretion of neurotrophic myokines and exosomes from skeletal muscle

Authors: *K.-Y. HUANG[1], H. KONG[2];
[1]Univ. of Illinois, Urbana-Champaign, Urbana, IL; [2]Chem. & Biomolecular Engin., Univ. of Illinois Urbana-Champaign, Urbana, IL

Abstract: Skeletal muscles are well known for enabling voluntary movement, yet they also crucially stabilize internal homeostasis and the functions of organs throughout the body. Skeletal muscles secrete a variety of peptides and cytokines, named myokines, which affect cells through autocrine, paracrine, and endocrine actions. Moreover, muscles produce extracellular vesicles such as exosomes, which hold promise in alleviating neurodegenerative conditions, Alzheimer's Disease included.
There is increasing evidence suggesting that individuals with neuromuscular disorders often suffer from issues that affect multiple organs, the immune system, and cognitive processes. These health concerns may stem from the altered secretion patterns of myokines and exosomes when neuromuscular junctions are damaged. Nonetheless, the precise processes at play remain elusive. Particularly in diseases featuring nerve damage, one pivotal question emerges: What role do motor neuron connections and activity play in the regulation of muscle secreting behavior? Our research proposes that the connections and activity of neurons are crucial in determining the release and functional impact of myokines and exosomes secreted by muscles. We engineered a two-dimensional muscle construct on both flat and micro-grooved polymer substrates to manipulate the extent of neural connections and muscular efficacy. Neural stem cells were then differentiated into motor neurons directly atop the muscle layer, prompting the formation of neuromuscular junctions. We evaluated how such neural interaction influences muscle contractions, the expression of genes linked to myokines, the secretion of myokines, and the

release of exosomes. Furthermore, we cataloged the miRNAs within exosomes sourced from both neuron-absent and neuron-innervated muscle tissue, exploring their impact on neural growth. Additionally, we explored how these muscle-derived factors promote the development, intercellular vesicle transport, and firing activity of cultured primary hippocampal neurons. Summarily, our investigation highlights the vital role of neuronal innervation in the modulation of skeletal muscle secretions, generating neuro-supportive myokines and exosomes with significant ramifications for in vitro nervous system cultures.

Disclosures: K. Huang: None. **H. Kong:** None.

Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.14/J29

Topic: I.04. Physiological Methods

Support: Bio & Medical Technology Development Program of the National Research Foundation funded by the Ministry of Science & ICT 2022M3E5E9016506
Bio & Medical Technology Development Program of the National Research Foundation funded by the Ministry of Science & ICT 2022M3C1A3091627
Korea Institute of Science and Technology Institutional Program under Project 2E33141

Title: Enhanced peripheral neural interface utilizing multi-intrafascicular shank array for high spatial selectivity; A rat model study

Authors: W. CHOI[1,2], H. PARK[1], S. OH[1,2], J.-H. HONG[3], J. KIM[3], D. YOON[2], ***J. KIM**[1]; [1]KIST (Korea Inst. of Sci. & Technology), Seoul, Korea, Republic of; [2]Sch. of Biomed. Engin., Korea Univ., Seoul, Korea, Republic of; [3]Dept. of Publ. Hlth. Sci., Korea Univ. Grad. Sch., SEOUL, Korea, Republic of

Abstract: The objective of this study is to design and validate a sophisticated multi-intrafascicular shank array neural interface tailored to peripheral nerves. The focus is on achieving superior spatial resolution, functional specificity and enhanced charge storage capabilities. The primary goal is to develop a neural interface that enables precise neuroanatomical mapping, neural signal acquisition and modulation. The methodology employed involves the design and development of the neural interface, which comprises 32 multi-channel working electrodes with enhanced charge storage capacity and reduced impedance. The integration of an insertion guide holder is used to refine neuronal targeting. Accurate electrode positioning, bipolar electrical stimulation and comprehensive assessment of evoked neural responses will be performed to determine the functionality of the device. Maintaining stability

over an eight-week period is critical to validating the reliability and longevity of the neural interface. This interface has been demonstrated to be highly effective in neuroanatomical mapping, with precise localization of motor nerves and successful elicitation of different movements. In two rats, various muscle movements were induced in 78.5% and 62.5% of the stimulated regions immediately after implantation of the device. Following implantation, the spatial resolution in the nerve was restored from 44.6% and 53.5% in week 1 to 67.8% and 69.6% in week 8 for the two rats, respectively. Sustained impedance stability over the eight-week period confirms the durability of the neural interface. Furthermore, this interface demonstrates its ability to capture sensory signals from different regions of the hind limb. In week 4 after implantation, 10 out of 32 channels (31.2%) yielded five different lower-limb sensory signals via the neural interface. The enhanced charge storage capacity and reduced impedance support the robust performance of the device, highlighting its potential for extended use. This research represents a significant step forward in neural interface technology, providing a versatile tool with wide-ranging application in neuroscience and neuroengineering. This interface's capacity to decode both motor and sensory neural activity positions it as a comprehensive solution for neuroanatomical investigations. Furthermore, the neural interface's precise neuromodulation potential holds promise for applications in advanced bionic prosthetic control and therapeutic interventions. The results of the study contribute to the growing field of neuroengineering, enabling improved understanding and manipulation of peripheral neural dynamics.

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Poster

PSTR351: Animal Models To Study Motor Units

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR351.15/J30

Topic: I.04. Physiological Methods

Support: NIH R01NS109237
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McKnight Foundation
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NIH R01NS084844
NIH R01NS099375
NIH R01EB022872
NSF 1822677

Title: Flexible EMG arrays with integrated electronics for scalable electrode density.

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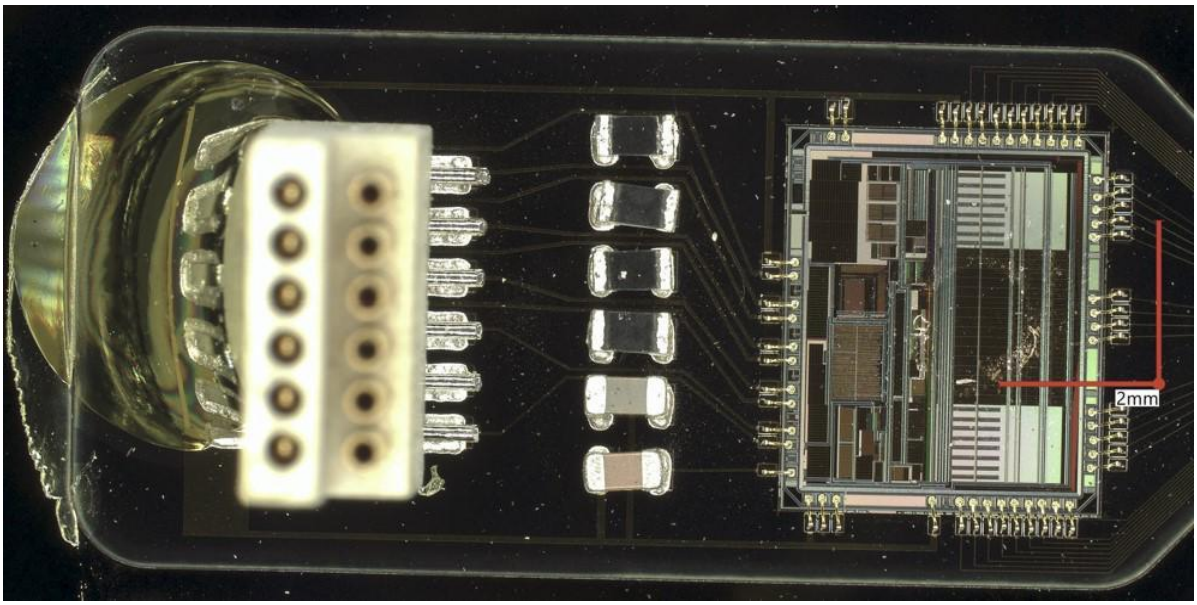
Abstract: Recent developments in electrode technology have demonstrated the power of flexible microelectrode arrays (FMEAs) for measuring muscle activity at high resolution. We recently introduced the Myomatrix array, a FMEA optimized for measuring the activity of individual motor units (the collection of motor units innervated by a single motor neuron; Chung et al, 2023) in freely behaving animals. Although FMEAs are fundamentally changing the way EMG is acquired, the number of recording channels is limited by the size of the plug that interfaces with the digital amplifier hardware and the density of electrode connections on the array. Increasing EMG channel count and supporting electrophysiological studies in smaller animals depends on two seemingly incompatible goals: reducing device size, while increasing the number of recording channels. The solution to this is to increase channel density, which is currently limited by requiring that separate headstage and FMEA components be used simultaneously. In our prior devices (Chung et al. 2023), each FMEA had a dedicated wire output for every electrode input, creating a channel density is 1:1. To improve this channel density, we have developed a novel device integrating a digital amplifier (bare-die RHD2216 chip, Intan, Inc.) directly onto an FMEA. This new design reduces the device's backend footprint by 74% and relocates the intan bare die from the headstage to the FMEA itself, creating a channel density of 1 : 3.2. Our methodology combines standard FMEA microfabrication with wire-bonding and surface-mounted components, enabling direct integration into a Serial Peripheral Interface (SPI) connection into the device itself, without any separate headstage. With this initial device we see a 1 : 3.2 channel density, but our method allows for using other bare die amplifiers (Intan, Inc.) for a channel density of 1 : 12.8. Our findings present a robust technique for chip embedding in custom FMEAs, applicable to in-vivo electrophysiology.



Disclosures: P. Anschutz: None. **M. Zia:** None. **J. Lu:** None. **M. Williams:** None. **A.L. Jacob:** None. **S.J. Sober:** None. **M. Bakir:** None.

Poster

PSTR352: Sexual and Social Communication Behaviors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.01/J31

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NSF Grant IOS-1946613
Wisconsin Alumni Research Foundation at University of Wisconsin-Madison

Title: Oxytocin impairs wound healing and increases sickness-induced affiliation in a social context-dependent manner

Authors: *E. R. HAMMOND[1], P. MONARI[2], A. P. AUGER[3], C. A. MARLER[4];
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Abstract: The role of oxytocin (OT) on social behavior is highly dependent on social context. For example, central OT signaling mediates prosocial interactions, such as nursing and affiliative touch, as well as agonistic interactions, such as social stress and aggression. OT has previously been demonstrated to have anti-inflammatory properties, but the relationship between social context and the anti-inflammatory properties of OT is understudied, especially in species that form highly affiliative bonds. In experiment 1, socially-housed and isolated male and female California mice received a small dermal wound as a localized immune challenge, and were assigned to receive either OT or saline i.p. every other day during wound healing. OT-treated isolated mice had larger wound sizes relative to OT-treated socially-housed mice, suggesting that OT effects on immune function may be social context-dependent. Moreover, higher levels of affiliative behavior were associated with reduced wound size. In experiment 2, we measured social preference and affiliation following treatment with OT, OT antagonist, or saline alone, under either a lipopolysaccharide (LPS) immune challenge or control saline. We found that in a mildly elevated inflammatory state induced by .1mg/kg i.p. LPS treatment, OT increased affiliative huddling behavior relative to saline treated mice, suggesting the context of inflammation influences the relationship between OT and social behavior. Additionally, we performed immunocytochemistry and are analyzing microglial activation in brain regions associated with social behavior to elucidate the relationship between immune activation in the brain, affiliative huddling, and OT. Taken together, these studies demonstrate that social context may play an important role on the function of OT on immune function, and that inflammatory state may similarly be important for the impact of OT on social behavior.

Disclosures: E.R. Hammond: None. **P. Monari:** None. **A.P. Auger:** None. **C.A. Marler:** None.

Poster

PSTR352: Sexual and Social Communication Behaviors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.02/J32

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NSF Grant IOS-1946613
NSF Grant DGE-1747503

Title: Long-term oxytocin signaling impairs communication and coordination in a monogamous rodent

Authors: *P. K. MONARI[1], E. HAMMOND[2], C. A. MARLER[2];
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Abstract: Interpersonal behavioral synchrony, a fundamental aspect of social interaction, is closely linked with efficient task accomplishment and social cohesion, with oxytocin (OXT) playing a pivotal role in its modulation. Little is known, however, regarding the enduring impact of adult chronic intranasal OXT treatment on behavioral synchrony. In the present study, we used the California mouse as an experimental model to examine chronic intranasal OXT-dependent changes in behavioral synchrony. Pair-bonded members of this monogamous and highly territorial species use a rich repertoire of ultrasonic vocalizations to flexibly coordinate goal-directed behavior across contexts. Adult females and males received a daily intranasal OXT infusion for 7 days, and were paired 3 weeks following the final treatment. Using automated detection of movement (DeepLabCut) and vocalizations (DeepSqueak), we examined the relationship between synchrony and chronic OXT in adult bonded pairs across various social contexts, including courtship, bond maintenance, and social challenge. Our study also explored the impacts of chronic OXT on the relationship between synchrony, communication, and birth outcomes, employing variational autoencoder-based unsupervised classification to identify new subsets of vocalizations and their associations with chronic OXT effects. Our major findings reveal that chronic OXT impaired courtship synchrony and altered the coordinated response to unfamiliar aggressive challenges post-pair bond establishment. Furthermore, chronic OXT induced changes in the number and type of vocalizations, suggesting modifications in communication patterns. Courtship vocalization diversity predicted pair success in the form of increased behavioral synchrony during bond maintenance, while average synchrony predicted pair fitness in the form of improved birth outcomes. Collectively, these results demonstrate the robust, enduring effects of chronic OXT on coordination and communication.

Disclosures: P.K. Monari: None. **E. Hammond:** None. **C.A. Marler:** None.

Poster

PSTR352: Sexual and Social Communication Behaviors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.03/J33

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: MH109302
MH110212
MH122622

Title: Non-synaptic oxytocin release modulates social communication by acting on vasopressin V1a receptors in Syrian hamsters

Authors: *D. ASPESI[1], J. C. WALTON[3], Z. GRIEB[2], M. KIRCHNER[4], Z. SONG[5], T. E. LARKIN, Jr.[6], J. E. STERN[7], H. ALBERS[8];
[1]Georgia State Univ., Atlanta, GA; [2]Georgia State Univ., Atlanta, GA, ; [3]West Virginia Univ., Morgantown, WV, ; [4]Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN, ; [5]Univ. of Minnesota, Minneapolis, MN, ; [6]CPFRC At Michigan Med., Ann Arbor, MI, ; [7]Content Mgmt. - AB 245, Atlanta, GA, ; [8]Georgia State Univ. Neurosci. Inst., Atlanta, GA

Abstract: Syrian hamsters engage in a form of social communication called flank marking, which is stimulated by social contact with other individuals and by the odors of other hamsters. Oxytocin (OT) and vasopressin (AVP) can act in the anterior hypothalamus (AH) to induce intense bouts of flank marking. OT and AVP can be released from synaptic regions of hypothalamic neurons, but also from non-synaptic areas such as axons, cell bodies, and dendrites. Non-synaptic release of OT and AVP is stimulated by calcium released from intracellular stores (iCa^{2+}) and can result in high concentrations of these neuropeptides that diffuse widely. Because of the high degree of similarity in the chemical structures of OT and AVP and their receptors there may be considerable cross-talk between these neuropeptides and their receptors. A significant gap in our knowledge is whether non-synaptically released OT or AVP play a critical role in regulating social behaviors such as flank marking and whether these effects are mediated by OT and/or AVP. First, we used an *in vitro* approach to determine if we could induce the non-synaptic release of OT but not AVP in a hypothalamic slice by administering α-melanocyte stimulating hormone (α-MSH). “Sniffer cells” capable of detecting OT or AVP found that administration of α-MSH induced OT and not AVP from the acute hypothalamic slices. To evaluate the role of non-synaptic OT release in flank marking, male and female hamsters were implanted with a cannula targeting the AH and subsequently tested for odor stimulated flank marking following the infusion of 360μM α-MSH into the AH. α-MSH increased flank marking in males and females, while the infusion of the α-MSH receptor (MC4R) antagonist MCL-0020 (900μM) suppressed flank marking in both sexes. Further, the injection of the iCa^{2+} antagonist TMB-8 (185.2nM) into the AH significantly inhibited odor-stimulated flank marking in response to α-MSH supporting the hypothesis that the actions of α-MSH within the AH were iCa^{2+}-dependent. Next, we examined if OT-mediated flank marking in response to α-MSH administration was due to the activation of AVP V1a receptors (V1aR) or OT receptors (OTR). Only the V1aR, and not the OTR antagonist, significantly reduced flank marking in male and female hamsters in response to α-MSH. These results support the hypothesis that flank marking is regulated by α-MSH-stimulated non-synaptic release of OT in the AH, and that OT acts on V1aRs to express flank marking in both males and females. These

are the first data to suggest that the physiological actions of OT can be mediated by V1aRs as well as OTRs and that non-synaptic release of neuropeptides are involved in the regulation of social behaviors.

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Poster

PSTR352: Sexual and Social Communication Behaviors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.04/Web Only

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Conahcyt CF-2023-G-289

Title: Oxytocin mediates Postpartum Estrous in Rats

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Abstract: Postpartum estrous (PPE) reaches its maximum level between 12 and 15 hours (h) after the birth of the first pup. It is known that similar to the intact rat, the sequential action of estradiol (E2) followed by progesterone (P4) elicits PPE (Connor and Davis, 1980a; Beyer et al., 2007). Once PPE females copulates with a male, they could be pregnant for a new litter and lactating the newborns (Connor and Davis, 1980a). Besides E2 and P4 there are other chemical compounds like oxytocin (OT) that elicits sexual behavior in cycling rats. Interestingly, OT is a hormone that induce uterine contractions along parturition and pups nipple sucking increases the levels of this hormone. Moreover, there is an increase in mRNA OT receptor levels in the brain at 9h after parturition (Medle et al., 2007). The present work explores the role of OT receptor of dams and sucking behavior by pups in PPE. For this purpose, we design two experiments. In the first one, we explore the role of OTR on PPE appearance. Therefore, at 11.5 h after the birth of the first pup, rats received OTR antagonist (atosiban n=10) or its vehicle (n=10). In the second experiment, we explore the effects of sucking behavior on PPE, for that reason pups were removed from their dams at birth (n=10) or let with them (control group, n=10 dams). The results suggest that OTR is related with PPE, because the group of dams that received atosiban expressed low levels of female sexual behavior compared with the control group. On the other hand, there were no statistical differences between the sucked dams and the females whose pups were removed. These findings suggests that OTR activation in essential for PPE appearance, and that other stimulus different to sucking behavior could contribute for PPE expression.

Disclosures: R. Domínguez Ordóñez: None. **G. Muñoz Castañeda:** None. **M. Garcia-Juárez:** None. **J.L. Encarnación Sánchez:** None. **O. González Flores:** None.

Poster

PSTR352: Sexual and Social Communication Behaviors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.05/J34

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant 2 U19 NS107616-06.

Title: Oxytocin's control of the hippocamposeptal neural circuit regulates recall of social hierarchy

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Abstract: Oxytocin (OXT) is a neuropeptide produced in the hypothalamus that plays central roles in reproduction, parental care, and emotion. However, its function in defined neural circuits controlling social dominance is not well understood. Historically, the lateral septum (LS) has been implicated in both suppressing and promoting aggressive behavior (Brady & Nauta, 1953; Leroy et. al., 2019). The LS receives downstream inputs from pyramidal neurons in hippocampal areas CA2 and CA3 (Cui et. al., 2013; Risold & Swanson, 1997). This circuit is enriched with oxytocin receptors (OXTR), and OXT signaling in the lateral septum is implicated in aggression (Freeman & Young 2016; Dhakar et. al., 2012). Our preliminary data shows that the LS is incredibly heterogeneous, which we hypothesize contributes to its complex control of social behavior. Here, we examine the role of OXT in ion channels, neuronal activity and synaptic transmission in the LS and a social ranking established by a tube test paradigm. The tube test is a well-accepted assay that assesses social dominance and hierarchy using round-robin competition among group-housed mice (Fan, Z. et al, 2019). We used an agent-based model to simulate changing social hierarchy dynamics following hippocampal system OXT disruption. The warm spot test was used as an additional dominance assay, and the two tests had roughly similar rankings. Manipulation of the oxytocin system in the LS was achieved using OXTR double-floxed (OXTR f/f) mice to assess the behavioral impact of brain-region specific OXTR knockdown. Injection of Cre-recombinase adenovirus into the LS of OXTR f/f mice perturbed stabilized tube test social rankings (n=6), followed by re-stabilization of altered social hierarchies (4/6). Meanwhile, GFP injection in wildtype controls left rankings unaffected (n=2), while GFP injection in OXTR f/f mice perturbed rankings which stabilized to similar or identical ranks as before (n=3). Our results suggest that OXT signaling in the LS is important for social recall. Since re-stabilized hierarchies are different after introduction of Cre, OXTR in LS neurons may be critical for reliable conveyance of hippocampally encoded social salience to brain structures that are downstream projection sites of LS. Future tests will aim to assess how

OXT disruption in one mouse changes its ranks to better assess the modulatory effects of OXT on dominance. Furthermore, the prevalence of increased aggression in Alzheimer's patients makes it worthwhile to determine whether OXT signaling is impaired in the context of amyloid or tau pathology.

Disclosures: G. Zhao: None. **K. Louie:** None. **J. liu:** None. **R.W. Tsien:** None.

Poster

PSTR352: Sexual and Social Communication Behaviors

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Topic: G.04. Emotion

Support: Kalman/AFAR Scholarship for Research in the Biology of Aging
R21NS125845
R56NS122351
RF1AG082478

Title: Oxytocin in the dorsomedial prefrontal cortex regulates empathy-driven consolation in mice

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Abstract: Impaired empathetic behaviors are prevalent in neuropsychiatric and neurodegenerative disorders; however, treatments remain limited and the underlying neural mechanisms are largely unknown. Consolation is an empathy-driven prosocial behavior aimed at comforting distressed conspecifics. Male and female rodents display allogrooming and body contact towards distressed conspecifics, leading to social buffering. Additionally, oxytocin receptor antagonism in the anterior cingulate cortex and chemogenetic inhibition of neuronal activity in the dorsomedial prefrontal cortex (dmPFC) reduce consolation. However, the mechanisms by which oxytocin mediates consolation remain unknown. To elucidate the neural mechanisms by which oxytocin regulates consolation, we performed behavioral, pharmacological, and neurophysiological experiments in adult C57BL/6J male and female mice. Compared to saline control, we found that systemic administration of the oxytocin receptor antagonist L-368,399 significantly reduced consolation towards distressed conspecifics, without impairing social investigation or emotional contagion. To assess the brain regions involved in consolation behavior, we conducted an activity-dependent c-Fos brain mapping assay and found that neurons expressing oxytocin receptors in the dmPFC were activated during consolation. We next administered L-368,399 into the dmPFC through implanted cannulae and found that oxytocin receptor antagonism in the dmPFC was sufficient to reduce consolation. To investigate whether oxytocin is released in the dmPFC during consolation, we injected an oxytocin sensor, $GRAB_{OT}$, and characterized oxytocin release dynamics in the dmPFC. Further, to assess how

oxytocin alters dmPFC neuronal function, and thereby regulate consolation behavior, we conducted slice electrophysiology and characterized the effects of oxytocin on membrane excitability, action potential waveform, and ion channel properties. These results suggest that oxytocin modulates consolation behavior through action in the dmPFC. Ongoing experiments aim to delineate the specific cell receptors and ion channels, synapses, and circuits that are modulated by oxytocin to promote consolation and to target these identified mechanisms to restore consolation in disease models.

Disclosures: A.M. Kobeissi: None. **W. Yao:** None.

Poster

PSTR352: Sexual and Social Communication Behaviors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Fundação para a Ciência e Tecnologia PTDC/NEU-SCC/4786/2014
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Champalimaud Foudation Internal Funds
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Title: A neuroanatomical substrate for the control of female sexual rejection

Authors: *I. C. DIAS[1], B. F. A. HUSAIN[2], L. FERREIRA[3], A. RASTEIRO[3], N. GUTIERREZ-CASTELLANOS[4], S. Q. LIMA[4];
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Abstract: Selecting an appropriate behavioral response in an internal state dependent manner is fundamental for well-being. Throughout the reproductive cycle, fluctuating levels of sex hormones coordinate female behavior with their reproductive capacity by modulating the activity of neuronal circuits expressing their specific receptors. Within the ventrolateral part of the ventromedial hypothalamus (VMHvl), neurons expressing receptors for sex hormones play a crucial role in female sexual receptivity. However, recent findings show that cellular, transcriptomic and functional properties of the VMHvl neurons are heterogeneous, varying along the anterior-posterior axis. While the progesterone-expressing neurons of the VMHvl (VMHvl.PR+) have been shown to be active when the female is receptive and mating, in our laboratory, using in vivo calcium imaging and optogenetics we show that the anterior VMHvl.PR+ neurons are involved in rejection behavior when the female is non-receptive. Using viral tracing techniques, we found that although both subpopulations strongly project to the

periaqueductal gray (PAG), their connectivity patterns into this midbrain structure differ across its anterior-posterior axis, with aVMHvl.PR+ neurons preferentially projecting to medial and posterior subregions, while the terminals of pVMHvl.PR+ neurons are detected posteriorly. Furthermore, the artificial activation of aVMHvl.PR+ neurons lead to activation of specific PAG subregions. Given the established role of the PAG in the control of opposing behaviors, such as escape and immobility, we hypothesize that the changes in female sexual behavior are in part controlled by the combinatorial action of the two PR+ populations on the PAG. We are currently testing this hypothesis by manipulating the activity of PR+ terminals in the PAG, hoping to further our understanding of such important behavior.

Disclosures: I.C. Dias: None. **B.F.A. Husain:** None. **L. Ferreira:** None. **A. Rasteiro:** None. **N. Gutierrez-Castellanos:** None. **S.Q. Lima:** None.

Poster

PSTR352: Sexual and Social Communication Behaviors

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Topic: F.02. Neuroendrocrine Processes and Behavior

Support: FCT PhD Fellowship (PD/BD141576/2018)
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Congento, co-financed by the Lisboa Regional Operational Programme (Lisboa2020), under the PORTUGAL 2020 Partnership Agreement

Title: Spinal control of copulatory behavior and sexual excitation

Authors: *A. P. MENDES[1], C. LENSCHOW[2], L. FERREIRA[1], B. LACOSTE[3], H. G. MARQUES[4], C. QUILGARS[5], S. BERTRAND[6], S. Q. LIMA[1];
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Abstract: Copulatory behavior increases male sexual excitation until the ejaculatory threshold is reached, allowing genital sensory input to trigger ejaculation. While copulatory behavior and sexual excitation are thought to be centrally regulated, ejaculation is a reflex controlled by a spinal circuit, whose activity is strongly inhibited by descending input from the brain, bearing no role on the regulation of copulation until the arousal threshold. However, this hypothesis remains untested. To tackle this problem, we combined genetics with electrophysiological and behavioral

analysis to functionally map the spinal circuit controlling the muscle involved in sperm expulsion, the bulbospongiosus muscle (BSM). We found that BSM motor neurons (BSM-MNs) receive direct synaptic input from a group of galanin-expressing (Gal+) interneurons located in the upper lumbar spinal cord. Furthermore, the spinal population of Gal+ neurons is progressively activated during copulation, and receives genital sensory input. Electrical and optogenetic activation of the Gal+ population evoked activity in BSM-MNs and BSM after spinalization. Interestingly, these effects were dependent on the sexual excitation state of the male and drastically decreased with repeated stimulation. Moreover, chemogenetic ablation of the Gal+ neurons severely impacted the latency to ejaculate and the structure of the copulatory sequence. Taken together, our results imply an unexpected involvement of the spinal cord in the control of copulatory behavior and sexual excitation, in addition to its well established role in ejaculation.

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Poster

PSTR352: Sexual and Social Communication Behaviors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.09/K1

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: CONACYT national scholarship 1159644

Title: Effect of the hypercaloric diet during pregnancy and lactation on the sexual behavior and brain dimorphic areas of adult male offspring

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Abstract: The diet we consume plays a vital role in maintaining our health. Given the current prevalence of high-calorie food consumption it is important to consider the long-term effects of hypercaloric diet during critical periods of brain development and on motivated behavior of the offspring, particularly during the transition into adulthood. Accordingly, we explored the effect of a hypercaloric diet during pregnancy and lactation on the sexual behavior and brain dimorphic areas of adult male offspring. Two grups of Wistar females were formed (n=5): 1) females fed with a cafeteria-type hypercaloric diet (HD, with +80% increase in calorie intake) and 2) control females that received standard laboratory feed (SD). Both groups received their diet throughout

an 8-week period that included 2 weeks prior to gestation, 3 weeks during gestation and 3 weeks of lactation. On PW12 (90 days) we assessed sexual behavior and one day later the brains were removed and stained using Nissl dye. The areas of the sexually dimorphic nucleus, ventromedial nucleus and amygdala were measured. Pups from HD mothers showed a higher frequency of ejaculations and a shorter latency to ejaculation, as well as a decrease in the size of the sexually dimorphic nucleus and amygdala. Our findings indicate that a maternal high-calorie diet has enduring effects on the expression of sexual behavior in adult male offspring, very likely affecting organization of the developing brain.

Disclosures: D. Rendón Coria: None. **G.A. Coria-Avila:** None. **M. Hernandez:** None. **G.E. Aranda-Abreu:** None. **F. Rojas-Durán:** None. **J. Manzo:** None. **R. Toledo-Cardenas:** None. **D. Herrera-Covarrubias:** None.

Poster

PSTR352: Sexual and Social Communication Behaviors

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Program #/Poster #: PSTR352.10/K2

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: University of Wisconsin-Stevens Point Research and Creative Activities Grant

Title: Effects of developmental exposure to Bisphenol-S on female and male sexual behaviors in rats

Authors: N. JOHNSON[1], M. C. KOPPLIN[2], K. POTTER[1], ***H. A. MOLENDA-FIGUEIRA**[3]; [1]Psychology, Univ. of Wisconsin - Stevens Point, Stevens Point, WI; [2]Psychology, Univ. of Wisconsin, Stevens Point, Stevens Point, WI; [3]Psychology, Univ. of Wisconsin-Stevens Point, Stevens Point, WI

Abstract: Bisphenols, such as Bisphenol-A, are a class of endocrine-disrupting chemicals to which humans are persistently exposed. While some bisphenols have been removed from major sources of exposure due to negative impacts on health including fertility, similar chemicals such as Bisphenol-S (BPS) have replaced them. To determine whether it is a safer alternative, we investigated the effects of developmental BPS exposure on sexual behavior in female and male rats as an indicator of neuroendocrine function. Long-Evans dams were paired with stud males on the day of estrus. BPS was administered orally at a dose of 50µg of BPS /kg body weight/day, beginning on the day of pairing and continued until parturition. Control dams receive saline. Offspring continued dosing until postnatal day (PN) 45 to encompass puberty, a developmental time point when disruption of hormone function negatively affects sexual behavior in rodents. Female offspring (BPS N=14, Control N=8) were assessed for estrous cyclicity for 15 days before ovariectomy, at PN90. Two weeks later, females were primed with 10µg estradiol benzoate followed 44 hours later by 500 µg progesterone to induce sexual receptivity and ensure

all females had equivalent circulating ovarian hormone levels. At PN104, females were paired with a male to assess lordosis posture frequency and intensity, as well as frequency of proceptive behaviors. Paired *t*-test were used to compare behavioral differences between BPS- and saline control-treated rats. Males' (BPS N=11, Control N=14) reproductive behaviors, including frequency of mounts, intromissions and ejaculations were also assessed. Each male received 6 sexual behavior tests with a hormone-primed sexually receptive female between PN120-140. Repeated measures ANOVAs will be used to compare behavioral differences between BPS and Control-treated males across tests. All behavior tests were video recorded for later evaluation by observers blind to treatment. Our study revealed no differences between BPS- and Control-treated females on measures of sexual receptivity or proceptive behaviors. Collection of data on males is currently in progress, but previous studies in which males received one test revealed no differences between treatment groups. However, many males fail to exhibit high levels of sexual performance during first pairings with receptive females. Therefore, following the sixth test, potential differences in performance may be revealed, which would also indicate sex-specific effect of BPS on sexual behavior. Alternatively, BPS may be determined to be a safer replacement for other bisphenols, warranting less concern for harm to reproductive function.

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Poster

PSTR352: Sexual and Social Communication Behaviors

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Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Technical support: Camacho F. and Ortiz J.
DGAPA/PAPIIT grants 207322 and IA208624..

Title: Kisspeptin and paced mating modulate resting state connectivity between brain regions of the social behavior network and reward system in female rats

Authors: *M. BEDOS[1], M. F. LÓPEZ-GUTIÉRREZ[2], R. G. PAREDES[2], S. ALCAUTER[2]; [1]Escuela Nacional de Estudios Superiores Unidad Juriquilla, Univ. Nacional Autónoma de México, Querétaro, Mexico; [2]Inst. de Neurobiología, Univ. Nacional Autónoma de México, Querétaro, Mexico

Abstract: Kisspeptin (kp) is a potent regulator of the hypothalamus-pituitary-gonads axis which is also involved in other processes outside the hypothalamus, namely the integration of sensory signals such as olfactory signals in rodents, and the processing of sexual and emotional information in humans. Importantly, we recently found that kp administered systemically induced a positive affective (PA) state and kp antagonist blocked the PA state induced by paced mating (PM). The aim of this study was to evaluate whether the systemic administration of kp or

PM modify the resting state (RS) connectivity in female rats. Therefore, we used sexually naïve Wistar female rats that were assigned to the following groups: a) kp, which received an i.p. injection of kp (14nmol/rat); b) paced (P), females were allowed to mate for 1h, pacing the sexual interaction; c) Non Paced (NP), females were allowed to mate without pacing the sexual interaction; d) Control (C), females were moved to the copulation box. All females were previously ovariectomized and induced to estrous by s.c. injections of estradiol benzoate and progesterone 48h and 4h before the tests, respectively. RS images were acquired 30min after either the injection of kp or the end of sexual behavior. Regions of interest related either to the reward system or the social behavior network were used to build connectivity matrices. NBS analysis (Matlab) revealed that treatments induced significant changes between the following nodes: medial amygdala (MeA), medial preoptic area (mPOA), anterior cingulate cortex (ACC), periaqueductal grey, ventromedial hypothalamus (VMH), arcuate nucleus (ARC) and ventral pallidum. Post-hoc analysis (FDR) showed that kp increased RS connectivity between brain areas that strongly express kp, such as ARC-MeA, ARC-mPOA and MeA-mPOA and decreased between ACC-ARC and ACC-VMH. We also found that NP mating decreased the RS connectivity between ACC-VMH. Further analyses including other ROIs as well as correlations with the behavioral data are planned.

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Poster

PSTR352: Sexual and Social Communication Behaviors

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Program #/Poster #: PSTR352.12/K4

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: CONAHCYT CF-2023-I-368
CONAHCYT 843707

Title: Is paracetamol a neuroendocrine disruptor of the sexual brain?

Authors: A. D. GUZMÁN MONTEMAYOR[1], J. J. SIERRA[1], G. ESPEJO-BERISTAIN[1], M. BARRADAS-MOCTEZUMA[1], A. A. CORONA-MORALES[2], L. I. GARCIA[1], J. MANZO[1], R. TOLEDO-CARDENAS[1], M. HERNANDEZ[1], D. HERRERA-COVARRUBIAS[1], ***G. A. CORIA-AVILA**[3];
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Abstract: Although paracetamol is considered a safe medication during pregnancy at therapeutic doses, and despite animal studies show no negative effects or report no adverse effects during pregnancy, there are no well-controlled clinical studies demonstrating its safety for both the

mother and fetus. Therefore, its use in this situation depends on the physician's discretion. Its mechanism involves the inhibition of the enzyme cyclooxygenase 2 and 3 (COX-2,3), which modulates pain. However, COX-2 is also part of the molecular cascade organizing the brain towards a male direction during the prenatal period, and potentially during other periods too. Herein, we explored the effects of paracetamol, a common medication used to treat fever and pain, as a neuroendocrine disruptor of the male sexual brain when administered during critical times of development such as pregnancy and the neonatal period. Thus, Wistar pregnant dams received 60 mg/kg s.c. of paracetamol or an equivalent volume of saline solution every 12 hours from gestational days 16-20. For neonatal males, paracetamol was administered in the same dosage during postnatal days 1-5. Then, rats were weaned and housed in groups of 4-5 until adulthood. At PND70, half of each group received exposure to receptive females, and the other half remained sexually naïve. At PD94, males were tested for anxiety-like behavior, at PND98 for sexual partner preference, and at PND100 their brains were processed for Golgi stain, Nissl, and Fos in the medial preoptic area. In addition, we assessed levels of testosterone and corticosterone in serum. Results indicated that prenatal administration of paracetamol for 5 days results in altered sexual partner preference in adulthood, affecting the genital investigations that males commonly perform on sexually receptive females. It also affected the time spent in physical contact with them, mounting and intromissions, and a reduction in the frequency and total time of visits. In many cases, rats treated with prenatal paracetamol did not explicitly show same-sex preference, but they lost interest in females. Many neurobiological variables indicated that prenatal paracetamol may disrupt the organization of the sexual brain, but sexual experience in adulthood appears ameliorate some of them.

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Poster

PSTR352: Sexual and Social Communication Behaviors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.13/K5

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: CONAHCyT SS 862263

Title: Affectation by gonadectomy of the muscle at the base of the penis in male rats with sexual experience previous.

Authors: *S. SANCHEZ[1], M. ALVARADO[2], J. RODRIGUEZ[3], G. A. CORIA-AVILA[4], L. I. GARCÍA[5];
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Abstract: Pelvic musculature has been widely studied for its involvement in both reproductive and non-reproductive processes. Particularly, it has been described that the bulbospongiosus muscle (mBs) plays a crucial role in the correct deployment of sexual behavior due to its anatomical location, as the mBs is located at the base of the penis and participates in seminal and urine expulsion. Therefore, its study is of paramount importance to understand different conditions. Our aim was to evaluate the effect of gonadectomy on the mBs of sexually experienced male rats. Sexually experienced male rats were used for this study, divided into three experimental groups to measure morphometric changes in the gross anatomy of the mBs (weight, length, width, and height), as well as histological changes in the muscle fibers composing the mBs. The results showed that the morphometry of the mBs increased in sexually experienced male rats. However, when gonadectomy was performed, muscle morphometry decreased. Additionally, an alteration in the cross-sectional area of the muscle fibers of the mBs was observed, possibly due to gonadectomy, as it affects the functionality of this musculature. Despite observing changes, these were not as drastic as those observed in other studies. In conclusion, prior sexual experience attenuates the effects caused by gonadectomy through frequent activation of the mBs. Finally, further specialized studies focused on measuring testosterone levels, as well as enzymatic analysis of muscle fibers, are suggested to identify the phenotype and predominant metabolism, to clarify these changes.

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Poster

PSTR352: Sexual and Social Communication Behaviors

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.14/K6

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIMH Grant R00MH11191

Title: Noncanonical genomic imprinting in monoaminergic pathways is involved in the regulation of social behaviors in mice

Authors: *E. M. O'LEARY, R. EGGLESTON, A. USMAN, A. L. TAMAS, S. KIM, D. D. MELING, P. J. BONTHUIS;
Univ. of Illinois Urbana-Champaign, Urbana, IL

Abstract: Genomic imprinting is an epigenetic process that differentially regulates the expression of maternally and paternally inherited alleles in offspring. Imprinted gene expression in the brain is theorized to provide parental control over offspring social behaviors. Canonically imprinted genes express one parental allele, either of maternal or paternal inheritance, while the

other allele is completely silenced. Noncanonically imprinted genes are defined as having one parental allele that has a higher expression bias at the tissue level when compared to the other allele. This bias can differ depending on tissue type and can even vary across anatomical domains within the same tissue. Tyrosine hydroxylase (*Th*) and dopa decarboxylase (*Ddc*) are noncanonically imprinted catecholamine synthesis genes with a maternal allele expression bias in the brain. TH and DDC are the first two enzymes in the pathway to produce dopamine (DA), norepinephrine (NE), and epinephrine (E); and DDC is also the second enzyme in the pathway to produce serotonin (5-HT). These neurotransmitters are critical regulators of social behavior and are therapeutic targets for human mental illnesses. *Ddc*'s imprinting patterns were found to be tissue and region-dependent with high maternal allele biased expression in the arcuate nucleus (ARN) and anteroventral periventricular nucleus (AVPV) of the hypothalamus, and a paternal allele bias in the peripheral catecholamine (NE and E) releasing adrenal medulla. Using reciprocal heterozygous mutant mice, we tested the functional impacts of *Ddc* maternally and paternally inherited alleles on sociability, maternal behavior, male sex behavior and aggression. We also sought to determine the cell-type specificity of *Ddc* imprinting in the brain, utilizing *Ddc* fluorescent reporter mice and fluorescent *in situ* hybridization to uncover whether *Ddc* noncanonical imprinting is limited to certain cell types in the brain and adrenal gland. We observed different effects of *Ddc* maternal versus paternal alleles on social behaviors. We then determined whether *Ddc* maternal allele biased expression exists in neurons, oligodendrocytes, and endothelial cell types in the brain. These findings show that in the monoaminergic synthesis pathway, noncanonical imprinted maternal and paternal alleles control different social behavioral roles which are likely determined by cell-type specific imprints. Altogether, these results highlight that the complex genetic architecture of maternally and paternally inherited alleles in monoaminergic pathways of the brain, and possibly even the entire organism, can have functional consequences on social behavior phenotypes.

Disclosures: E.M. O'Leary: None. **R. Eggleston:** None. **P.J. Bonthuis:** None.

Poster

PSTR352: Sexual and Social Communication Behaviors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.15/K7

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Coordinated neural activity over the maternal transition: exploring maternal electrical dynamics and the impact of early life stress

Authors: *S. MITCHELL[1], M. MATKOVICH[1], M. EBERLE[2], H. E. STEVENS[3], R. HULTMAN[2];
[1]The Univ. of Iowa, Iowa City, IA; [2]Mol. Physiol. and Biophysics, The Univ. of Iowa, Iowa City, IA; [3]Psychiatry, The Univ. of Iowa, Iowa City, IA

Abstract: The maternal brain undergoes successive change over pregnancy and postpartum. While these alterations have been linked to behavioral responses beneficial to offspring, they may also have negative maternal outcomes. This investigation examines changes in brain-wide electrical dynamics in the maternal brain, both in relation to maternal time course and maternal behavior. Specifically, this study utilizes previously identified stress-associated electrical brain networks known as "*Electome Factors*" (*EF*s) to examine how coordination of neural activity changes with maternal experience. Maternal vulnerability may be heightened by adverse experiences, such as prior early life stress (ELS). ELS impacts depression and anxiety associated neural pathways, which largely overlap with those underlying maternal displays. Therefore, *EF*s were also examined according to ELS history. A combination of maternal separation with limited nesting material and early weaning was used as a model of ELS in CD1 mice (n=19-21 litters/group). For the continued observation of brain-wide electrical dynamics, pregestational adult female mice were surgically implanted with multi-site in vivo recording electrodes. Recordings included the following brain regions: prelimbic and infralimbic cortices, nucleus accumbens, basolateral, medial, and central amygdala, ventral hippocampus, ventral tegmental area. Recordings were captured in the home cage and after a forced interaction task (FIT) at pregestational through weaning stages, thus gaining network observations spanning the full course of maternal brain change (n=12-14/group). Maternal behaviors were recorded for assessment alongside electrical dynamics. Gene expression and microglia in these same brain regions were also examined (n=10-14/group). Postpartum animals had heightened activity of a previously characterized stress-associated, depressive network during the FIT which was further elevated in ELS mothers (AUC = 0.7647). The activity of other stress-associated *EF*s was additionally found to be associated with maternal behavioral states. The prefrontal cortex (PFC) and amygdala form a circuit underlying trait vulnerability and significant effects of parity (p=0.0091) and ELS (p=0.0078) were found in PFC reactivity (8-11Hz) of this circuit during the FIT. Furthermore, PFC microglia were altered by ELS and related gene expression change studies are in progress. This study demonstrates that not only does coordinated neural activity change in the maternal brain in relation to maternal care, but it may also underlie stress vulnerability.

Disclosures: S. Mitchell: None. **M. Matkovich:** None. **M. Eberle:** None. **H.E. Stevens:** None. **R. Hultman:** None.

Poster

PSTR352: Sexual and Social Communication Behaviors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR352.16/K8

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Neurons in apMPOA regulate male sexual behavior

Authors: *M. WANG, Y. XU;
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Abstract: Nutrition and sex go arm by arm, yet the underlying neurobiological mechanisms are unclear. Central estrogen receptor estrogen receptor α (ERα) and leptin receptor (LepRb) signaling sense nutritional signals and modulate sexual behavior. Thus, we hypothesized that ERα in LepRb-expressing neurons coordinates nutrition and sexual behavior. We generated mice with deletion of ERα specifically in LepRb-expressing neurons ($ER\alpha^{\Delta LepRb}$ mice). Male $ER\alpha^{\Delta LepRb}$ mice displayed significantly impaired sexual behavior such as decreased mean intromission time and impaired ejaculation. Female $ER\alpha^{\Delta LepRb}$ mice displayed strikingly sexual rejection indicated by a significantly increased number of rejection behaviors (fleeing, boxing, kicking, rearing). Therefore, ERα in LepRb neurons is required for normal sexual function. In addition, we found that leptin reversed fasting-induced sexual dysfunction only in male controls, while loss of ERα in LepR neurons blunted this rescue effect. Dieting-induced weight loss in obese mice rescued the intromission time in male controls but not $ER\alpha^{\Delta LepRb}$ mice, indicating this effect also required the ERα in LepR neurons. These findings suggest that ERα in LepRb neurons coordinates nutrition and male sexual behavior. Then we stereotaxically injected the Cre-dependent Adeno-associated virus carrying the ERα in the anteroventral and periventricular portion of the medial preoptic area (apMPOA). Surprisingly, the ERα restoration only in the apMPOA region was sufficient to rescue the mean intromission time in male $ER\alpha^{\Delta LepRb}$ mice. We further found that the activity of $apMPOA^{LepRb}$ neurons was associated with engagement in male sexual behavior and inhibition of the $apMPOA^{LepRb}$ neurons significantly suppressed the male sexual behavior. Together, our results indicate that apMPOA ERα and LepRb are critical in male sexual behavior.

Disclosures: M. Wang: None. **Y. Xu:** None.

Poster

PSTR353: Stress and Neuroimmunology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.01/K9

Topic: F.03. Stress and the Brain

Support: Herman Dana Foundation

Title: Childhood trauma cortisol and immune cell glucocorticoid transcript levels are associated with increased risk for suicidality in adolescence

Authors: *T. GOLTSER[1,2], R. SEGMAN[1,2];
[1]Mol. Psychiatry Lab., Hadassah Med. Organization and Fac. of Med., Hebrew Univ., Jerusalem, Israel; [2]The Herman-Danna Division of Pediatric Psychiatry, Department of Psychiatry, Hadassah - Hebrew University Medical Center, Jerusalem, Israel

Abstract: Rising adolescent suicide rates present a major unmet need. Childhood trauma (CT) has been associated with altered cortisol dynamics and immune cell glucocorticoid reactivity, yet their additive longer-term contributions to later suicide outcomes are less clear. The current study

compared CT scores, resting salivary free cortisol and mononuclear cell gene expression levels of the nuclear receptor, subfamily 3, member 1 (NR3C1) coding the glucocorticoid receptor, and its co-chaperons FKBP prolyl isomerase 5 (FKBP5) and KIT Ligand (KITLG), between a cohort of adolescents presenting with a suicidal crisis requiring hospital treatment, and matched healthy controls. Childhood trauma scores and glucocorticoid measures were significantly altered among suicidal adolescents, and CT scores correlated with mononuclear cell glucocorticoid transcripts. Both CT scores and glucocorticoid measures explained substantial additive portions of the variance in adolescent suicidality. Long-term perturbations in cortisol dynamics and immune cell glucocorticoid response elements denote dysregulated immune stress reactivity, and may possess value in prediction and point to modifiable-risk factors in prevention of clinically significant suicidality during the brittle period of adolescence, years after childhood trauma exposure.

Disclosures: T. Goltser: None. **R. Segman:** None.

Poster

PSTR353: Stress and Neuroimmunology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.02/K10

Topic: F.03. Stress and the Brain

Support: This research project was supported by the AEIRC Pakistan [grant number 0527/KHI/AG/R&D/2019].
PROF DR. Richard Sherman for his invaluable guidance and support throughout the duration of this study

Title: Examining the Impact of Guided Disclosure Protocol on Post-Traumatic Growth: A Randomized Control Trial Investigating Psychophysiological Changes among Individuals with Traumatic Stress

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Abstract: Title: **Examining the Impact of Guided Disclosure Protocol on Post-Traumatic Growth: A Randomized Control Trial Investigating Psychophysiological Changes among Individuals with Traumatic StressShamoon Noushad[1,2,3] , Sadaf Ahmed[1,] Basit Ansari[3], Ujala Sajid[1,2]**1. Department of Physiology, Psychophysiology Research Lab, University of Karachi2. Department of Psychology, Malir University of Science and Technology3. Department of Health, Physical Education & Sports Sciences, University of KarachiCorresponding author email: shamoon@aeirc-edu.com
AbstractThe differentiation between traumatic stress and Post-Traumatic Growth (PTG) is debated, and the psychophysiological relationship between them is not fully understood. This

randomized control trial aimed to investigate the impact of Guided Disclosure Protocol (GDP) on PTG and associated psychophysiological changes in individuals with traumatic stress. Participants were randomized into intervention (GDP) and control groups, and completed questionnaires at baseline and 3 months post-intervention. Psychophysiological measures, including C-Reactive Protein, Brain Derived Neurotropic Factor, Interleukin-6, Cortisol, Heart Rate Variability, and brain waves, were assessed. The results showed that the intervention group experienced a significant increase in PTG, as evidenced by declines in Trauma Symptom Checklist and Traumatic Stress Scale scores. However, there were no significant changes in heart rate, heart rate variability, or biochemical measures. After 3 months of intervention, there was no significant difference in PTG scores or traumatic stress symptoms between the intervention and control groups. In conclusion, the GDP was found to significantly increase PTG in the intervention group, but no significant changes were observed in physiological and biochemical measures. These findings suggest that GDP may be effective in promoting PTG in individuals with traumatic stress, but further research is needed to fully understand the psychophysiological relationship between traumatic stress and PTG.
Keywords: Guided Disclosure Protocol, Post-traumatic Stress, Post-traumatic Growth, Traumatic Stress, Psychophysiological Measures.

Disclosures: S. Noushad: None. **S. Ahmed:** None. **B.P. Ansari:** None. **U. Sajid:** None.

Poster

PSTR353: Stress and Neuroimmunology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.03/K11

Topic: F.03. Stress and the Brain

Support: NIH Grant R01AT010005

Title: Where the rubber meets the road: A randomized placebo-controlled trial of an immunomodulatory probiotic intervention for Veterans with PTSD

Authors: *C. A. LOWRY[1], K. A. STEARNS-YODER[2], C. E. STAMPER[3], A. J. HOISINGTON[4], D. P. BROSTOW[4], C. A. HOFFMIRE[5], J. E. FORSTER[4], T. T. POSTOLACHE[6], L. A. BRENNER[7];
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Abstract: Data suggest that chronic low-grade inflammation may be a risk factor for development of posttraumatic stress disorder (PTSD) following trauma exposure, as well as a

contributor to persistent post-traumatic symptoms. The “Old Friends” hypothesis proposes that chronic low-grade inflammation, particularly in modern urban environments, is due to reduced exposures to diverse microbial inputs with which humans coevolved. Consequently, one strategy for treatment of PTSD may be exposure to probiotic organisms with anti-inflammatory and immunoregulatory properties. Here we investigated the effects of an immunoregulatory probiotic on psychological (PTSD) symptoms and biological signatures of systemic inflammation among United States Veterans from recent conflicts. Specifically, we explored the effects of daily oral administration of *Lactobacillus rhamnosus* GG (LGG; ATCC 53103), a probiotic shown to have beneficial anti-inflammatory and immunoregulatory effects, for eight weeks. This Phase IIa trial of an immunoregulatory probiotic supplementation is being implemented using a longitudinal, double blind, randomized placebo-controlled design. As recommended for clinical trials in psychiatry exploring effects of anti-inflammatory interventions, this trial selectively enrolled individuals with elevated biomarkers of inflammation [Miller and Raison, 2015, JAMA Psychiatry 72:527-528]. Specifically, we enrolled individuals with plasma C-reactive protein (CRP) > 1.0 mg/L, measured using a high-sensitivity CRP assay, as an inclusion criterion. Individuals are being randomized to placebo or probiotic supplement, stratified by sex. At present, 82 individuals of the target goal of 100 participants have completed the trial, and it is expected that the final participants will complete the study by the end of summer 2024. Findings could support larger and rigorous randomized controlled efficacy trials for civilians and Veterans with PTSD, with the goal of decreasing symptoms and improving function.

Disclosures: C.A. Lowry: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Probiotic and placebo capsules were supplied by Chr. Hansen, part of Novonesis. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Founder, Board Member, and Chief Scientific Officer of Mycobacteria Therapeutics Corporation. **K.A. Stearns-Yoder:** None. **C.E. Stamper:** None. **A.J. Hoisington:** None. **D.P. Brostow:** None. **C.A. Hoffmire:** None. **J.E. Forster:** None. **T.T. Postolache:** None. **L.A. Brenner:** None.

Poster

PSTR353: Stress and Neuroimmunology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.04/K12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: This work is supported by a grant from the Department of Defense (W81XWH-20-1-0568 to A.K.S.)

Title: Brain Inflammation in Veterans with Gulf War Illness Could be Tracked by Analyzing Microglia-derived Extracellular Vesicles in the Blood

Authors: *A. K. SHETTY[1], L. N. MADHU[1], P. PANDA[1], L. ORLINSKY[2], K. SULLIVAN[2], K. K. AENLLE[3];

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Abstract: Cognitive dysfunction, neuroinflammation, and systemic inflammation are observed in veterans afflicted with Gulf War Illness (GWI). Enhanced concentration of proinflammatory markers in the blood may also be due to brain inflammation, as inflammatory proteins from brain cells can enter the blood through vesicles shed by these cells into the extracellular space. These extracellular vesicles (EVs) are membrane-enclosed nanosized vesicles that carry a cargo comprising proteins, miRNAs, and lipids. EVs from brain cells are seen in the blood because they can easily cross the blood-brain barrier. Because the composition of EVs reflects the physiological or pathological state of cells from which they are derived at the time of secretion, analysis of EVs derived from specific brain cells in the blood would help identify biomarkers linked to brain impairments. This study investigated the extent and mechanisms of brain inflammation in veterans with GWI through a liquid biopsy approach. Multiple biomarkers related to neuroinflammation, oxidative stress, and complement activation were analyzed through ELISAs in neuron-derived EVs (NDEVs), astrocyte-derived EVs (ADEVs), and microglia-derived EVs (MDEVs) isolated via immunocapture methods from the serum samples of veterans with GWI (GWI group, n=31) or controls without GWI (control group, n=13). The results demonstrated that NDEVs and ADEVs getting into the blood do not carry increased levels of proinflammatory and complement-activation-related proteins or oxidative stress markers in veterans with GWI compared to veterans without GWI. However, MDEVs getting into the blood carry increased concentrations of multiple proinflammatory and complement-activation-related proteins in veterans with GWI compared to veterans without GWI, suggesting that microglia are likely the primary mediators of chronic neuroinflammation and complement activation in the brain of veterans with GWI. Furthermore, the upregulation of proinflammatory and complement activation markers differed between MDEVs and whole serum, with MDEVs displaying upregulation of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, IL17a, complement 3 (C3), and C1q and whole serum exhibiting upregulation of only IL-6 and IL17a, implying that analysis of MDEVs offers a better assessment of brain inflammation than whole serum analysis. Overall, the results highlight that neuroinflammation gleaned from the analysis of MDEVs is much higher than systemic inflammation gleaned from whole serum analysis in veterans with GWI. Additionally, increased complement activation seems to be restricted to the brain in veterans with GWI.

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Poster

PSTR353: Stress and Neuroimmunology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.05/K13

Topic: F.03. Stress and the Brain

Title: Fli-1 Regulates CD4 T cell activation in Veterans with PTSD

Authors: P. LI[1], L. LIU[1], Z. WANG[2], ***H. FAN**[3];
[1]Pathology and Lab. Med., Med. Univ. of South Carolina, Charleston, SC; [2]Ralph H. Johnson VA Med. Ctr., Charleston, SC; [3]Pathology and Lab. Med., Med. Univ. of South Carolina Neurosci., Charleston, SC

Abstract: Post-traumatic stress disorder (PTSD) is a debilitating psychiatric disorder characterized by re-experiencing, avoidance, negative emotions and thoughts, and hyperarousal. Among Veterans who served in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) and utilize the VA Health Care System, the incidence of PTSD is estimated at 24.7%. Current treatment options for PTSD demonstrate limited efficacy, with only half of combat Veterans responding positively. Consequently, there is an unmet need to gain a deeper understanding of PTSD pathology to enable the development of alternative therapeutic strategies. Emerging research suggests a role for immune dysregulation in the pathology of PTSD, marked by elevated levels of inflammatory mediators. However, the specific underlying mechanisms of immune imbalance are not well understood, and there is limited research exploring methods to restore immune homeostasis in PTSD. We obtained PBMCs from Veterans with PTSD and control groups, with both groups exhibiting similar levels of combat exposure in the OEF/OIF conflicts. We observed a significant upregulation of Fli-1 expression in the PBMCs from Veterans with PTSD compared to the control group. This elevation in Fli-1 levels was predominantly found in the $CD4^+$ T cell, with no significant alteration in $CD8^+$ T cells. Upon stimulation with lipopolysaccharide (LPS), PBMCs from the PTSD group exhibited elevated Fli-1 expression and increased levels of inflammatory cytokines such as IL-6, and IFN-γ compared to the controls. To suppress Fli-1 expression, we developed an antisense oligonucleotide Gapmer, which effectively reduces Fli-1 levels in both human and mouse cells. Treatment of PTSD PBMCs with Fli-1 Gapmers resulted in a significant reduction in inflammatory cytokine levels, restoring them to levels of the control Veteran group. These findings suggest the potential of Fli-1 suppression in reinstating immune homeostasis in PBMCs from Veterans with PTSD. Furthermore, employing a co-culture model of PBMCs from both control and PTSD Veterans with the human brain microglia cell line HMC3, we observed increased levels of inflammatory mediators such as IL-6, and IFN-γ in HMC3. Intriguingly, when HMC3 cells were co-cultured with PTSD PBMCs treated with Fli-1 Gapmers, there was a significant reduction in inflammatory mediator levels compared to those treated with control Gapmers. These findings suggest that Fli-1 suppression may restore immune balance within PBMCs and mitigate microglial activation in the brain, potentially paving the way for innovative therapeutic interventions.

Disclosures: P. Li: None. **L. Liu:** None. **Z. Wang:** None. **H. Fan:** None.

Poster

PSTR353: Stress and Neuroimmunology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.06/K14

Topic: F.03. Stress and the Brain

Support: State Key Laboratory of Brain and Cognitive Sciences

Title: Exploring the impact of social isolation on neuroimmune responses and neurons

Authors: *X. YE, G. LEUNG, R. CHANG;
Sch. Biomed. Sci., Lab. of Neurodegenerative Dis., LKS Fac. of Med., Univ. of Hong Kong, Hong Kong, China

Abstract: Social isolation is a social problem, especially during the pandemic and for the elderly. More than 30 years ago, social isolation had been suggested as a major risk factor for mortality, the development of smoking habits, obesity, high blood pressure, depression, anxiety disorders, and dementia. However, the underlying mechanism remains poorly investigated. Opportunistic infection often occurs in people with social isolation, which in turn synergizes depressive symptoms. Our laboratory has shown that infection or body injury can rapidly stimulate neuroimmune responses. Therefore, we use mice as an experimental model to investigate whether neuroimmune responses underlie the mechanism of social isolation-induced depression. Here we show that after eight weeks of social isolation, we observed significant depressive symptoms in 18-month-old male mice ($p < 0.0001$, $n = 7$-8), with higher expression of complement factor 3 in the hippocampal astrocytes ($p = 0.0134$, $n = 7$-8). We also observed a significant reduction in the mRNA expressions of Netrin 4 and p21-activated kinase 3 ($p = 0.0104$ and $p = 0.0003$, $n = 7$-8) in the hippocampus, suggesting altered synaptic functions. Socially isolated mice also responded differently to lipopolysaccharide (LPS) compared to group-housed mice. These changes particularly involved the axon guidance and glutamatergic pathways that are implicated in synaptic plasticity. Taken together, these results suggest that eight weeks of social isolation is sufficient to induce depressive symptoms and changes in synaptic plasticity, and socially isolated subjects are more prone to neuronal network remodeling after peripheral LPS challenge.

Disclosures: X. Ye: None. **G. leung:** None. **R. Chang:** None.

Poster

PSTR353: Stress and Neuroimmunology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.07/K15

Topic: F.03. Stress and the Brain

Support: K01 MH117343
Tulane Start-up Funds
Tulane Brain Institute

Title: B LYMPHOCYTE PRESENCE EXERTS TIME- AND SEX-SPECIFIC IMPACTS TO BLOOD-BRAIN BARRIER INTEGRITY FOLLOWING SINGLE RESTRAINT STRESS EXPOSURE IN MICE

Authors: L. WEGROWSKI[1], I. PURSELL[2], N. BARAHONA[3], R. FREITAS[2], ***E. B. ENGLER-CHIURAZZI**[3];
[1]Univ. of Manchester, Manchester, United Kingdom; [2]Neurosurg., Tulane Univ., New Orleans, LA; [3]Tulane Univ., New Orleans, LA

Abstract: Bidirectional communication between the central nervous system and immune system modulates immune responsiveness and influences neurological disorder pathogenesis, neuroinflammation, and mood regulation. Recent studies underscore T lymphocytes' role in stress responses and disorders, yet the contribution of B lymphocytes remains largely understudied. Expanding on our previous findings that revealed tissue-specific differences in B lymphocyte subsets under acute stress, specifically an increase in B1a cells and a decrease in marginal zone precursor cells in the brain, our study aimed to explore B lymphocyte migration to the brain using a single 6 hour restraint stress paradigm in C57BL/6 and B lymphocyte knockout (BKO) mice. We examined corticosterone levels at tissue collection alongside key blood-brain barrier (BBB) proteins, ZO-1 and Occludin. ZO-1 anchors proteins to the cell's structure, whereas Occludin physically seals the space between cells, both of which contribute significantly to BBB integrity. Groups included non-stressed (Control) mice and those euthanized immediately after stress (DOS), 3-4 days post-stress, or 7 days post-stress. For both males and females, analysis of corticosterone levels indicated non-significant interaction effects but significant main effects for genotype and stress, with BKO mice exhibiting elevated corticosterone levels indicating a potential role of B lymphocytes in modulating the stress response. Analysis for females revealed significant differences between control, DOS, and 7 days post-stress ($p < 0.05$), and between DOS, 3-4 days, and 7 days post-stress ($p < 0.0002$). Males showed significant differences between control, 3-4 days, and 7 days post-stress ($p < 0.05$), as well as DOS, 3-4 days, and 7 days post-stress ($p < 0.0044$). In protein analysis of prefrontal cortex tissue, ZO-1 showed a significant genotype effect ($p=0.03$), with wild-type mice having lower expression than BKO mice. However, a distinct visual trend was observed in male wild-type mice, showing a decline in ZO-1 expression following stress. In both WT and BKO male mice, Occludin levels remained stable. This could suggest that B cell presence is necessary for stress-induced changes in BBB integrity; follow-up experiments to discern the extent of BBB permeability. For females, no significant differences with genotype were found. Overall, the findings suggest that prefrontal cortex BBB integrity may vary depending on B cell presence and sex during stress. Future research will investigate neuroinflammatory states and neuronal damage to uncover the mechanisms that drive the migration of distinct B cell subsets to the brain.

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Poster

PSTR353: Stress and Neuroimmunology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.08/K16

Topic: F.03. Stress and the Brain

Support: IMSS grant FIS/IMSS/PROT/PRIO/19/109

Title: Neuroimmune responses to stress in the hippocampus of adult rats is conditioned by the neonatal stressor suffered

Authors: *L. TORNER[1], L. M. SAAVEDRA- PIMENTEL[2], M. A. ROQUE[3,4];
[1]Biomed. Res. Ctr., Mexican Inst. of social security IMSS, Morelia, Mexico; [2]Ctr. de Investigación Biomédica de Michoacán, Inst. Mexicano Del Seguro Social, Morelia, Mexico; [3]Neurobio., Ctr. de Investigación Biomédica de Michoacán, Morelia, Mexico; [4]Instituto de Investigaciones en Recursos Naturales, Universidad Michoacana de San Nicolas de Hidalgo, Morelia, Mexico

Abstract: Early life stress is known to increase the risk of psychiatric illnesses in adulthood. Immune stressors such as severe neonatal infections also contribute to the development of affective diseases. Emotional and immune stressors trigger immediate activation of the neuroimmune system and result in emotional alterations in adulthood. Here we compared the long-term effects of neonatal maternal separation (MS) and immune challenge (LPS) alone or combined on cytokine expression in the hippocampus of adult rats under basal or stress conditions. Sprague Dawley rats were used: 1) Control + Veh; 2) maternal separation (MS, 3h/day from postnatal [PN] 1 to 14) +VEH; 3) Control + Lipopolysaccharide (LPS, 0.5 mg/kg, PN14); 4) MS + LPS. At PN 140, the animals were euthanized under basal conditions or 3 h after stress (10 min forced swim). The hippocampi were extracted, homogenized and the RNA was isolated to subsequently analyze the expression of cytokines by qPCR. We found that the expression of TNFα was not changed in any of the groups under basal conditions, but it was increased in the MS+VEH group under stress conditions. Expressions of IL-1β and IL-6 were significantly increased under both basal and stress conditions only in the MS+VEH group. The expression of IL-10 was increased in the MS+VEH group only under basal conditions but decreased in the MS+LPS group after stress. These results indicate that the expression of some pro- and anti-inflammatory cytokines remain increased long term in the group that suffered the emotional stressor alone (MS). However, MS followed by neonatal LPS challenge (second hit) showed an attenuated expression after a new stressor in adulthood (third hit). Likewise, MS group shows an exacerbated cytokine response to the next stressor in adulthood, but not the other groups. In conclusion, the stress – induced neuroinflammatory response of the hippocampus is selective to the type and number of adverse events faced in early stages. Few differences were found between males and females. Funded by Instituto Mexicano del Seguro social (IMSS) through Fundación IMSS (grant number FIS/IMSS/PROT/PRIO/19/109).

Disclosures: L. Torner: None. **L.M. Saavedra- Pimentel:** None. **M.A. Roque:** None.

Poster

PSTR353: Stress and Neuroimmunology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR353.09/K17

Topic: F.03. Stress and the Brain

Support: NIH DK124727
NIH GM060507
NIH MD006988
LLUSM GRASP Seed Funds

Title: Synaptic Vesicle 2A-Microglia Interactions in Early Life Adversity-Induced Binge Eating

Authors: *T. SIMON[1], P. ONTIVEROS-ANGEL[2], J. SIERRA[1], V. WILLIAMS[1], G. WRIGHT[1], A. WILLIAMS[1], A. RHEE[1], J. D. FIGUEROA[3];
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Abstract: Binge eating (BE) in response to early life adversity is a highly prevalent maladaptive coping strategy observed in individuals struggling with obesity as they seek relief from psychological distress. Early-life adversities such as social isolation (SI) promote aberrant brain maturation and emotional dysregulation associated with BE. Synaptic vesicle 2A (SV2A) is a critical coordinator of experience-dependent brain communication and maturation. SV2A dysfunction is strongly implicated in several mental health disorders and obesity. Convergent neuroimaging data in psychiatric and obese humans demonstrates deficits in SV2A radioligand signal in corticolimbic brain regions. Although these connections are recognized, the role of SV2A in maladaptive BE remains unknown. Furthermore, how SI impacts naturalistic behaviors throughout adolescence and how those changes precipitate BE in adulthood is unknown. We hypothesize that stabilizing SV2A levels will reduce SI-induced BE behaviors in rats. Adolescent Lewis rats (n=64; half-females) were assigned to either the Paired group (two rats per cage) or the Isolated group (one rat per cage), with isolated rats being reared in individual cages during adolescence. Rats underwent emotionality tests and a three-week intermittent Western-like diet access paradigm. In the third week, Paired and Isolated groups received Levetiracetam (LEV, 10 mg/kg) or Vehicle. LEV is an antiseizure treatment known to bind to SV2A. We used fluorescent in-situ hybridization to examine synapses and microglial-phagocytic markers in the hippocampus. A subset of Isolated (n=12) and Paired rats (n=12) were 1. placed in the PhenoTyper Homecage Monitoring System during adolescence (weekly for seven weeks) to measure the effect of SI on naturalistic behaviors and calculate composite phenotypic z-scores; or 2. used for longitudinal μPET imaging to measure ^{18}F-SDM-8-SV2A levels in SI males and females. Results indicate that SI rats exhibited elevated emotionality compared to Paired controls. Longitudinal assessments revealed SI-induced deviations in phenotypic z-scores beginning at week 2 and highlighted behaviors predictive of Western-like diet binging in adulthood. Hippocampal *SV2A* levels were reduced in female SI animals. SI increased microglia (Iba1)-phagocytic (CD68) markers. LEV treatment reduced BE in SI females. Finally, μPET showed stark increases in ^{18}F-SDM-8-SV2A radioligand measurements in the hippocampus of adolescent SI females compared to age-matched males. This study marks progress in identifying

maladaptive BE mechanisms and developing predictive behavioral biomarkers for disordered eating.

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Poster

PSTR353: Stress and Neuroimmunology

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Topic: F.03. Stress and the Brain

Support: TCU CSE Science & Engineering Research Center (SERC) Grant

Title: Impact of food insecurity on behavior and inflammatory response in old-age C57BL/6J mice

Authors: *L. P. K. GUNDERSON[1], M. BERTRAND[2], M. J. CHUMLEY[2], G. W. BOEHM[1]; [1]Psychology, [2]Biol., Texas Christian Univ., Fort Worth, TX

Abstract: Over 6 million households with children in the U.S. suffer from food insecurity, the majority of which are insecure without hunger. Food insecurity and the accompanying chronic unpredictability are associated with significant negative physical health outcomes, such as malnutrition and impaired immune function, and psychological health outcomes, such as anxiety/eating disorders and delayed language acquisition. To better understand the connection between the unpredictability of a food source and cognitive/immunological impairments, prior studies have attempted to model food insecurity in rodent models. An ideal study design to get at this question would use a truly unpredictable food source and assess both behavioral and immunological changes in the rodents following insecurity, but most of the prior work has not been able to address all three of these features and thus are limited in the generalizability of their findings. To address these limitations, the present study aimed to ensure that the rodent's food source was truly unpredictable and that both behavioral and immunological variables were measured to draw conclusions about the true impact of insecurity. 18-month-old male and female C57BL/6J mice were either given ad libitum food access or were food insecure, where two nights were randomly selected during the week in which their otherwise full food-hopper would be reduced to 25% of their baseline consumption until the following morning. At 21 months, the mice underwent a battery of behavioral tests, including the open field test, elevated-zero maze, and novel object location task, to assess anxiety-like behavior and spatial memory capabilities. Further, brain tissue was collected to quantify the amount of soluble amyloid-β in the cortex and the amount of pro-inflammatory cytokines such as TNF-α and IL-6 in the hippocampus and cerebellum. Taken together, these findings provide a more complete analysis of the behavioral and immunological changes resulting from a truly unpredictable food source which more closely represents the environment of those living with food insecurity.

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Poster

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Program #/Poster #: PSTR353.11/K19

Topic: F.03. Stress and the Brain

Title: One-hour isolation stress alters corticolimbic mrna expression of stress, clock, and proinflammatory immune factors in pae female adolescent mice.

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Abstract: INTRODUCTION: Fetal alcohol spectrum disorder (FASD) stems from prenatal alcohol exposure (PAE), affecting 1-5% of the US population and correlates with heightened anxiety disorders. Susceptibility involves maladaptive stress responses in the central nervous system (CNS) with consequent heightened proinflammatory cytokine reactivity in corticolimbic regions like the prefrontal cortex (PFC), amygdala (AMG), and hypothalamus (HYP) that are critical for mood regulation. Adolescence is a period of stress susceptibility. Stress triggers corticotropin-releasing hormone (CRH), the cytokines IL-1β, TNFα and related immune factors NFκB and NLRP3, which may influence circadian clock regulators Per1 and Per2, whose dysregulation in corticolimbic regions is linked to clinical anxiety. However, the impact of stress-induced CNS immune factors and clock genes on corticolimbic stress responses during adolescence remains largely unexplored. Therefore, we hypothesize that adolescent mild, single stress alters the corticolimbic expression of proinflammatory and clock genes. METHODS: Postnatal day (PND) 38-44 C57BL/6 female mice with PAE or control exposure, whereby dams were exposed to saccharin (SAC; 0.066%)/water or SAC-sweetened (0.066%) ethanol (10% w/v) 4hrs daily prior to breeding and during gestation, were used. SAC controls and PAE offspring underwent a single, 1hr isolation stress, with tail vein blood (~70µl) collected before and after isolation. Anxiety was assessed during isolation by time spent along the isolation chamber borders vs. center zones, and jumping activity. At 24hrs post-isolation, the PFC, AMG, and HYP were dissected. Plasma corticosterone (CORT) was assayed by ELISA. Transcriptional expression of CRH, NFκB, NLRP3, IL-1β, TNFα, Per1, and Per2 mRNA was analyzed using RT-qPCR.RESULTS: During isolation stress, both SAC- and PAE-treated mice remained at the field's border; however, SAC-exposed mice exhibited significantly more initial jumping activity

vs. PAE-exposed mice. Stress-induced CORT was significantly increased in isolated mice. In the AMG of PAE mice, NFκB and NLRP3 mRNA levels were blunted, while IL-1β, Per1, and Per2 were elevated. In the HYP of PAE mice, Per1 and Per2 were blunted, with no changes in NFκB, NLRP3,
IL-1β, and TNFα. A significant interaction between stress and prenatal treatment was observed in CRH and NLRP3 in the hippocampus and the PFC, respectively.CONCLUSIONS: PAE alters responses to mild stress, by dysregulated gene expression of proinflammatory factors and clock regulators, which renders adolescent corticolimbic regions susceptible to stress-induced reprogramming and anxiety disorders.

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Poster

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Topic: F.03. Stress and the Brain

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Title: Chemokine receptor 5 signaling in PFC mediates stress susceptibility in female mice

Authors: *H.-Y. LIN[1,2], F. CATHOMAS[3], L. LI[3], R. DURAND-DE CUTTOLI[3], K. CHAN[3], L. F. PARISE[3], C. YUAN[4], A. V. AUBRY[3], J. ALVAREZ[3], R. FISHER[3], S. J. RUSSO[3], J. WANG[5,6];
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Abstract: Chronic stress induces changes in the periphery and the central nervous system (CNS) that contribute to neuropathology and behavioral abnormalities associated with psychiatric disorders. In this study, we examined the impact of peripheral and central inflammation during chronic social defeat stress (CSDS) in female mice. Compared to male mice, we found that female mice exhibited heightened peripheral inflammatory response and identified C-C motif chemokine ligand 5 (CCL5), as a stress-susceptibility marker in females. Blocking CCL5 signaling in the periphery promoted resilience to CSDS. In the brain, stress-susceptible mice displayed increased expression of C-C chemokine receptor 5 (CCR5), a receptor for CCL5, in microglia in the prefrontal cortex (PFC). This upregulation was associated with microglia

morphological changes, their increased migration to the blood vessels, and enhanced phagocytosis of synaptic components and vascular material. These changes coincided with neurophysiological alterations and impaired blood-brain barrier (BBB) integrity. Blocking CCR5 signaling specifically in the PFC were able to prevent stress-induced physiological changes and rescue social avoidance behavior. Our findings are the first to demonstrate that stress-mediated dysregulation of the CCL5-CCR5 axis triggers excessive phagocytosis of synaptic materials and neurovascular components by microglia, resulting in disruptions in neurotransmission, reduced BBB integrity, and increased stress susceptibility. Our study provides new insights into the role of cortical microglia in female stress susceptibility and suggests that the CCL5-CCR5 axis may serve as a novel sex-specific therapeutic target for treating psychiatric disorders in females.

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Poster

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Topic: F.03. Stress and the Brain

Title: Chronic stress promotes peripheral immune interactions at the brain endothelium

Authors: *J. ALVAREZ[1], F. CATHOMAS[2], H.-Y. LIN[2], K. CHAN[2], L. F. PARISE[2], A. RAMAKRISHNAN[2], M. ESTILL[2], R. L. FISHER-FOYE[1], S. J. RUSSO[2];
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Abstract: Chronic psychosocial stress is a significant risk factor for the development of stress-associated psychiatric disorders, including major depressive disorder, which causes profound debilitation and has increasing worldwide prevalence. Pre-clinical and clinical studies have linked peripheral immune system alterations to stress-related disorders, including elevated levels of proinflammatory immune cells and cytokines in circulation. Endothelial cells are critical components of the blood-brain barrier (BBB), as they interface directly with immune cells and their released factors, which can enter the brain parenchyma to regulate local neural activity. Current research suggests region-specific differences in brain endothelial permeability, which may be related to differences in the local production of chemoattractants and adhesion molecules for immune cells following chronic psychosocial stress. A causal mechanistic understanding of how these changes occur in stress-responsive brain regions, including the nucleus accumbens (NAc), is not fully demonstrated. To address this gap, endothelial cell mRNA was collected from the NAc of male mice following chronic social defeat stress (CSDS) using translating ribosome affinity purification. Following RNA sequencing and analysis, we observe that CSDS strongly affects NAc endothelial cells, such that stress-susceptible male mice display an increased

expression of genes associated with endothelial cell junction organization and adhesion. Current work aims to validate the upregulation of these genes and virally manipulate their expression to determine their involvement in immune cell recruitment to the endothelium and BBB permeability. This work will uncover unique mechanisms through which endothelial cells respond to chronic stress and provide insight for developing novel therapeutics for stress-associated psychiatric disorders.

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Poster

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Topic: F.03. Stress and the Brain

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Title: Stress-activated brain-gut circuits disrupt intestinal barrier integrity and social behavior

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Abstract: BACKGROUND: Major depressive disorder (MDD) represents the leading cause of disability, affecting over 300 million people worldwide. Largely characterized behaviorally, it is critical to identify biological changes associated with MDD. Emerging literature recognize a correlation between MDD and chronic low-grade inflammation; however it is not fully known how this inflammation is initiated. Recently, several inflammatory conditions have been associated with increased intestinal permeability. We hypothesize that chronic psychosocial stress disrupts gut barrier integrity, allowing translocation of gut microbial byproducts into circulation, triggering systemic inflammation associated with depression-like behavior. METHODS: To capture behavioral and biological changes relevant to human psychiatric

disorders in an animal model, we used the 10-day chronic social defeat stress (CSDS) paradigm in mice. We subsequently measured gut inflammation by flow cytometry, and intestinal permeability by orally gavaging mice with FITC-Dextran. To identify neurocircuitry regulating stress-induced intestinal pathophysiology, we used retrograde tracing and chemogenetic strategies to manipulate brain-gut circuits.
RESULTS: Mice exposed to CSDS showed increased pro-inflammatory Th1 cells and decreased anti-inflammatory Th2 cells in the colon compared to unstressed control mice. Moreover, stressed mice exhibited greater intestinal permeability, along with elevated circulating lipopolysaccharide (LPS) levels. Using retrograde tracing from the enteric neurons in the colon, we found that corticotropin-releasing hormone (CRH)-expressing neurons in the paraventricular nucleus of the hypothalamus (PVH) innervate the gut. Further, using chemogenetic activation or inhibition of PVH CRH+ neurons, we found that these neurons can regulate intestinal inflammation, barrier permeability, and social avoidance behavior induced by CSDS.
CONCLUSIONS; Collectively, our results illustrate a brain-gut circuit where stress activates specific neurons in the brain to trigger intestinal inflammation and disrupt intestinal barrier function, potentially promoting depression-like behavior.

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Poster

PSTR353: Stress and Neuroimmunology

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Topic: F.03. Stress and the Brain

Support: NIH Grant R01MH127820

Title: Neurobiological underpinnings of stress-induced social reward deficits

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Abstract: Diminished social interaction is a hallmark behavior in numerous psychiatric diseases, including major depressive disorder, and has been linked to increasing suicide rates in recent years. However, the neurobiological mechanisms underlying altered prosocial behavior remain poorly understood. Utilizing a preclinical model of social trauma in mice, the chronic social

defeat stress (CSDS) model, we aim to elucidate the brain-wide neurobiological mechanisms contributing to social deficits. To explore social investigation and social avoidance we use a resident intruder (RI) task. The RI task involves measuring the social behaviors of our experimental mice by introducing a novel juvenile social partner to their home cage. To explore social reward and motivation we use a social self-administration (SSA) task. The SSA task involves fixed ratio active lever pressing to gain access to a novel juvenile mouse behind a mesh barrier. We also use the SSA task to investigate social reward deficits with a progressive ratio design, where there is a gradual increase in the number of correct responses needed to receive a social reinforcement. We identified alterations in brain reward circuitry following CSDS, highlighting the Anterior Cingulate Cortex (ACC) as a central node involved in social interaction during the RI task through whole-brain clearing and imaging. Our data also indicated reduced SSA performances in CSDS-exposed mice, suggesting broader deficits beyond classical social avoidance. This research provides new insights into the neurobiological basis of social anhedonia, a critical symptom across various stress-induced psychiatric disorders.

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Poster

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Title: Involvement of the projections from lateral habenula to RVM in the social defeat stress-induced behavioral impairments

Authors: *M. PAGLIUSI, Jr.[1,2], R. DURAND-DE CUTTOLI[3], J. ALVAREZ[4], R. L. FISHER-FOYE[4], H. OH[3], H.-Y. LIN[3], F. V. GOMES[5], S. J. RUSSO[3];
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Abstract: Although chronic pain is not among the symptoms of depression, epidemiological studies indicate a close association between depressive disorder and chronic pain. Chronic social defeat stress (CSDS), which involves a resident-intruder paradigm, has been widely used to induce negative affective states that models some symptoms of both depression and chronic pain. Using the CSDS paradigm, we recently described a novel function of the rostral ventromedial

medulla (RVM) on stress-related behavioral impairments. We showed that the activation of the RVM during defeat sessions prevented social avoidance, chronic pain, anhedonia, and learned helplessness induced by CSDS. Further, the inhibition of the RVM induced a susceptible phenotype after a subthreshold social defeat stress. The RVM is a key structure of the descending pain pathway, acting as an important relay for other brain structures such as the anterior cingulate cortex (ACC) and lateral habenula (LHb). In this study we aimed to investigate the involvement of these RVM targeting projections in stress response. We first monitored the activity of these projections during behavior using fiber photometry and, using optogenetics we activated the axon terminals in the RVM of each projection during behavioral analysis. The behavioral tests performed in this study were the social interaction, elevated plus maze, von Frey filament, and capsaicin, collectively encompassing a comprehensive range of behaviors. Though the present data is preliminary, early analyses suggest that LHb-RVM projections play important roles in CSDS outcomes, being implicated in the pain behavior but not in depression-related behavior. Our results highlight the RVM as a significant neural hub of interest for both depression and chronic pain, serving as a neuroanatomical substrate that interconnects these two conditions.

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Poster

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Title: Social recognition requires TRIM28-mediated transcriptional regulation in mouse prefrontal cortex

Authors: *R. K. KIM[1], C. SMITH[2], N. L. TRUBY[2], G. M. SILVA[3], J. A. PICONE[2], P. J. HAMILTON[4];
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Abstract: Social behaviors are integral components of the health of the individual and contribute to cohesive group living. Yet, the molecular mechanisms that govern social behaviors, and how they are impacted in disease states, remain poorly understood. Recent studies investigating neuropsychiatric syndromes have identified regulatory mechanisms of transposable elements (TE) as a promising area of exploration to understand the biological basis of social dysfunction. Here, we present a synthetic biology approach to comprehensively assess the social behavioral effects of *TRIM28* within mouse prefrontal cortex (PFC). *TRIM28* is a Krüppel associated box (KRAB) associated protein known to repress TEs through chromatin silencing mechanisms involving zinc finger proteins (ZFP). To directly interrogate the transcriptional function and behavioral consequences of *TRIM28*, we reprogrammed endogenous *TRIM28*^{WT} by replacing the histone methyltransferase recruiting domain with an enhanced transcriptional activation domain VP64-p65-Rta (*TRIM28*^{VPR}), or by excising the functional domains entirely (*TRIM28*^{NFD}). In a luciferase reporter assay with a promoter containing ZFP binding sequences in cultured Neuro2a cells, we observed that *TRIM28*^{VPR} resulted in significantly higher luciferase signal in a ZFP-dependent manner compared to *TRIM28*^{WT} and *TRIM28*^{NFD} ($p<0.0001$). Following Herpes virus-mediated delivery of these variants to mouse PFC, we applied a variety of behavior tests to clarify the impact of *TRIM28*-mediated transcriptional control on mouse behavior against an *HSV-GFP* control. *HSV-TRIM28*^{WT} and *HSV-GFP*-treated mice displayed normal sociability and preference for novel interaction on 3 chamber social interaction (3CSI), and *HSV-TRIM28*^{NFD} showed a trend of preference for novel interaction ($p=0.0121$, 0.0051, 0.0796 respectively). However, *HSV-TRIM28*^{VPR} mice displayed no preference for a novel mouse in 3CSI ($p=0.9170$), despite equivalent total time spent interacting with targets. Further, only *HSV-TRIM28*^{VPR} mice displayed inability to participate in social hierarchies in dominance tube testing, with dominant and subordinate mice reverting to a random chance of victories following PFC transduction ($p=0.0070$ and 0.0422 respectively). We found no change in anxiety-like behaviors on open field or elevated plus maze, suggesting the observed disruption in social behaviors may be due to an inability to recognize and distinguish other mice in social settings rather than reduced interest in socialization. We have submitted PFC tissue for RNA sequencing to interrogate the transcriptional mechanisms driving these observed social deficits.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

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Program #/Poster #: PSTR354.01/K26

Topic: F.07. Biological Rhythms and Sleep

Support: NIH Grant R37-HD081168

Title: Parafacial zone and frontal cortex exhibit parallel homeostatic responses to sleep deprivation

Authors: *M. AHMAD, G. SOKOLOFF, M. S. BLUMBERG;
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Abstract: Beginning around 12 days of age (P12) in infant rats, the amount of quiet (or NREM) sleep begins to increase at the expense of active (or REM) sleep. This developmental increase in quiet sleep is accompanied by the sudden emergence of a cortical delta rhythm (0.5-4 Hz). We recently discovered that, as cortical delta emerges, the parafacial zone (PZ), a medullary structure implicated in the regulation of quiet sleep, exhibits a local delta rhythm coherent with cortical delta; moreover, PZ neurons fire together in a rhythmic pattern that is phase-locked with the trough of PZ delta. These and other features of PZ delta indicate that it is a medullary homologue of cortical delta. Because homeostatic regulation of cortical delta in response to sleep deprivation is one defining characteristic of quiet sleep in adults, we assessed whether homeostatic regulation of delta is also observed in PZ. To do this we deprived P12 rats (n=8) of sleep for 30 minutes while recording from PZ and frontal cortex. To deprive pups of sleep predominantly during quiet sleep, whenever delta was observed in either brain region, we roused them using a cold stimulus applied to the thermoreceptive region of the snout. This method reliably and rapidly produced intense sleep pressure, as operationalized by the increased rate of application of the cold stimulus over the deprivation period. Pups were then allowed to sleep undisturbed for an additional 60 minutes. Early in the recovery period (0-30 min), deprived pups exhibited pronounced increases in PZ and cortical delta power; late in the recovery period (30-60 min), delta power had returned to levels seen at baseline. Sleep deprived pups showed increased quiet sleep duration during recovery. Control pups (n=8) exhibited no such changes in sleep duration or delta power. A follow-up experiment will determine whether these parallel homeostatic responses in PZ and cortex are similarly affected by inactivation of the median preoptic nucleus, a hypothalamic region that mediates homeostatic responses in the adult cerebral cortex. The demonstration of parallel homeostatic responses in PZ and cortex provides additional support for the hypothesis that these two delta-rhythmic structures are part of a single sleep-regulatory system.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

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Topic: F.07. Biological Rhythms and Sleep

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FBM UNIL Doctoral Fellowship
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Title: Abstract Title: Noradrenergic locus coeruleus activity functionally partitions NREM sleep to gatekeep the NREM-REM sleep cycle

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Abstract: The noradrenergic *locus coeruleus* (LC) is vital for brain states underlying wakefulness. During non-rapid-eye-movement sleep (NREMS) in mice, activity levels of LC neuronal populations fluctuate on an infraslow time scale of ~50 s. Moreover, LC activity in sleep has also been associated with rapid-eye-movement sleep (REMS) and arousability control. To date, whether LC activity fluctuations have a broader relevance for the dynamics of sleep and its functions remains to be determined.To monitor and manipulate the activity of LC neurons during sleep, we conditionally expressed genetically encoded Ca^{2+} sensors, GPCR activation-based NE sensors and/or optogenetic actuators in dopamine-b-hydroxylase-(DBH)-Cre mice. We then combined fiber photometry and/or closed-loop optogenetics with polysomnography in undisturbed sleep but also under REM sleep restriction or various sleep deprivation protocols.We demonstrate that the activity of LC during uninterrupted sleep is highly dynamic. During NREM sleep, its activity transiently reaches values comparable to wakefulness, whereas it drops to minimal levels upon transitions to REM sleep. Those natural LC fluctuations rule the time scales over which the NREMS-REMS cycle evolves, setting the moments when transitions between NREMS and REMS are permitted. This ruling involves the alternation between high and low LC activity levels that associate with distinct signatures at the autonomic, subcortical and cortical arousal levels. This alternation divided the NREMS-REMS cycle into sequential intervals of ~50 s. REMS was possible only when a ~50-s interval had completed and LC activity reached low levels, as evident by repeated ~50-s long NREMS-REMS cycles during REMS restriction. In addition, a stimulus-enriched wake experience was followed by a more fragmented NREMS and by delayed REMS, which could be antagonized by LC optogenetic inhibition.Our findings illustrate a distinct function of the LC in controlling mammalian sleep, acting as a subordinate neural mechanism that regulates the duration of the NREMS-REMS cycle susceptible to induced disruptions due to prior wake experiences.

Disclosures: G. Foustoukos: None. **A. Osorio-Forero:** None. **R. Cardis:** None. **N. Cherrad:** None. **L.M. Fernandez:** None. **A. Luthi:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.03/K28

Topic: F.07. Biological Rhythms and Sleep

Support: U.S. Department of Defense grant W911NF1910280
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Tiny Blue Dot Foundation

Title: Hippocampal sharp wave sleep: a unifying view of sleep in the hippocampus

Authors: *G. FINDLAY[1,2,3], M. CAVELLI[4,2], T. BUGNON[5], W. MARSHALL[6,2], G. TONONI[5], C. CIRELLI[5];
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Abstract: How is neural activity in the hippocampus affected by sleep loss, and does the hippocampus accumulate and discharge sleep need differently from cortex? We investigated these questions by performing continuous 48-hour sleep/wake Neuropixels recordings from posterior parietal cortex and dorsal hippocampus in 16 freely moving rats (Sprague Dawley males). Recordings included 24h of undisturbed baseline followed by 6h of sleep deprivation and 18h of recovery. Each rat underwent up to 3 separate 48h recordings, each with a different type of sleep deprivation: first using novel objects, next using forced locomotion (8 rats), and finally a combination of both (5 rats). We find that hippocampal sharp waves (SPW) robustly reflect sleep need: their rate and amplitude increase over the course of extended wake (first 1h vs last 1h, post-hoc tests on a linear mixed effects model after confirming significant main effect, corrected for multiple comparisons, $p < 0.05$) and decrease during sleep. Ripples and dentate spikes (DS) show similar homeostatic changes. Such homeostatic regulation is strongly reminiscent of cortical slow wave activity (CX-SWA). Like CX-SWA, we find that hippocampal markers of sleep are sensitive to the rat's behavior during extended wake. For instance, cumulative theta:delta ratio during wake predicts SPW amplitude during early recovery sleep ($p < 0.05$, all experiments). Also, for most hippocampal markers of sleep need (SPW rate and amplitude, DS rate and amplitude, and ripple rate), increased expression during extended wake is associated with decreased expression during early recovery sleep, suggesting that the former can substitute for the latter. For all hippocampal markers of sleep need the magnitude of homeostatic rebound (its level during early recovery sleep, minus its level during baseline sleep matched to the same circadian time) does not positively correlate with SWA rebound, suggesting that the hippocampus accumulates and discharges sleep need independently of cortex. Finally, we find that 1s epochs containing SPW are always associated with an elevated hippocampal slow-to-fast gamma ratio—believed to reflect a more disconnected, internally-oriented state of the hippocampus—even during wake ($p < 0.05$). Thus, we find that SPW-rich periods are characterized by the two fundamental features of sleep: partial disconnection and homeostatic regulation, even when they occur during cortical wake. We refer to this disconnected, homeostatically regulated, unitary state as "hippocampal sharp wave sleep," by analogy to cortical slow wave sleep.

Disclosures: G. Findlay: None. **M. Cavelli:** None. **T. Bugnon:** None. **W. Marshall:** None. **G. Tononi:** None. **C. Cirelli:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

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Topic: F.07. Biological Rhythms and Sleep

Support: NIH P01 HL149630.

Title: Activation of medullary serotonergic cell subtypes differentially modulates breathing, upper airway tone, and arousal threshold during sleep as relevant for sleep-disordered breathing

Authors: *P. SABERI[1], K. LEHIGH[2], A. TRAN[1], S. M. DYMECKI[2], V. G. VANDERHORST[1];
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Abstract: Sleep-disordered breathing (SDB), a spectrum of conditions affecting breathing during sleep, occurs due to defects in: upper airway patency, respiratory drive, and/or arousal threshold. These functions are largely modulated by brainstem circuits. Caudal brainstem serotonergic neurons are necessary for increasing respiratory response to hypercapnia during wake (Ray et al., 2011). These serotonergic neurons represent at least 2 subtypes, *Tac1-Pet1* and *r5Egr2-Pet1* neurons as named by molecular expression (Okaty et al., 2015). *Tac1-Pet1* neurons innervate motor regions, including phrenic and upper-airway muscle projecting hypoglossal motor neuron pools, and the rhythm-generating pre-Bötzinger complex (Hennessy et al., 2017). *r5Egr2-Pet1* neurons, which are intrinsically chemosensitive, project mainly to sensory areas including nucleus of the solitary tract, retrotrapezoid nucleus, and parabrachial nucleus (Brust et al., 2014). Here, we set out to investigate their distinct roles in modulation of respiration, upper airway tone, and arousal threshold during sleep. The project was approved by the IACUC. We used adult triple transgenic *Tac1-Cre; Pet1-Flpe; RC::FL-hM3Dq* mice and *Egr2-Cre; Pet1-Flp^e; RC::FL-hM3Dq* mice of both sexes, which expressed the activating M3 Designer Receptor Exclusively Activated by Designer Drugs in *Tac1-Pet1* and *Egr2-Pet1* neurons, respectively. They were instrumented for EEG, genioglossus (GG), and neck muscle EMG to measure sleep/wake state and muscle tone, and measured breathing in a whole-body plethysmograph. We exposed mice to normocapnia, continuous hypercapnia, and repeated intermittent hypercapnia after either saline or clozapine-N-oxide (CNO, the ligand for hM3Dq) i.p. injection. We analyzed data pertaining to NREM sleep and arousal from NREM sleep using each mouse as its own control. Results showed that during NREM sleep, activation of *Tac1-Pet1* neurons increased GG and neck muscle activity in normo- and hypercapnia, while ventilation increased only during hypercapnia compared to the control condition. *Tac1-Pet1* neuron activation did not change the hypercapnia-induced arousal response. In contrast, activation of *Egr2-Pet1* neurons shortened the latency to hypercapnia-induced arousal, but did not modulate EMG activity or ventilation in normo- or hypercapnia compared to the control condition. We conclude that increased activity of both *Tac1-Pet1* and *Egr2-Pet1* neurons modulated breathing, upper airway tone, and latency to arousal during sleep, but through contrasting cell type-specific mechanisms. These findings raise the possibility of selectively targeting these neurons to ameliorate SDB.

Disclosures: P. Saberi: None. **K. Lehigh:** None. **A. Tran:** None. **S.M. Dymecki:** None. **V.G. VanderHorst:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

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Program #/Poster #: PSTR354.05/K30

Topic: F.07. Biological Rhythms and Sleep

Support: UNAM, DGAPA, PAPIIT IN201424

Title: Influence of irregular photoperiod on circadian locomotor activity, feeding profile, and hypothalamic preproorexin expression in lean Neotomodon alstoni mice.

Authors: *M. MIRANDA-ANAYA[1], M. REVUELTAS GUILLEN[2], E. ARELLANES-LICEA[3];
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Abstract: Circadian desynchronization is implicated in irregular activity and feeding patterns associated with the development of obesity. In the *Neotomodon alstoni* mouse, throughout its lifespan, a subset of individuals remains lean while others develop obesity linked to disrupted circadian rhythms, characterized by alterations in motor activity and feeding behavior. We aimed to investigate whether exposure to an irregular photoperiod over three months induces circadian disruption that may alter locomotor activity distribution and feeding patterns, potentially leading to metabolic changes assessed by glucose tolerance. Additionally, we explored the possibility of observing a correlation with the pre-proorexin gene expression in the hypothalamus. Adult lean male *N. alstoni* mice (12-14 months old, n= 24) were raised and kept in vivarium conditions. One group was maintained under a standard LD 12:12 photoperiod, while a second group was exposed to a zig-zag light schedule consisting of three days of 2-hour advances followed by three days of consecutive delays, and a shift to reset the photoperiod in the control group. Individual locomotor activity was assessed using infrared light crossings, and food intake along with feeding behavior over 24 hours was recorded monthly. After 12 weeks of irregular lighting cycles, no significant changes were observed in body weight, although the experimental group exhibited reduced locomotor activity and extended food intake during the daytime. Expression of the pre pro-orexin gene in the hypothalamus during the nighttime phase showed a tendency to decrease compared to controls. These findings suggest that exposure to irregular photoperiods impacts daily locomotor activity rhythm and disrupts feeding behavior, but not body weight.

Disclosures: M. Miranda-Anaya: None. **M. Revueltas Guillen:** None. **E. Arellanes-Licea:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.06/K31

Topic: F.07. Biological Rhythms and Sleep

Title: Effect of Transcutaneous vagal nerve stimulation (tVNS) on sleep architecture in healthy, young adults.

Authors: *A. SUBRAMONIAM[1], G. GILMORE[2], L. WHITEHURST[3];
[1]Biol., Univ. of Kentucky, Lexington, KY; [2]Univ. of Kentucky, LEXINGTON, KY; [3]Univ. of Kentucky, Lexington, KY

Abstract: Effect of Transcutaneous vagal nerve stimulation (tVNS) on sleeparchitecture in healthy, young adults.Authors Anjana Subramoniam[1], Gabe Gilmore[2], Lauren Whitehurst[21]Dept. of Biology, College of Arts and Sciences, University of Kentucky, KY[2]Dept. of Psychology, College of Arts and Sciences, University of Kentucky, KY**Abstract**Sleep is a universal, multi-faceted behavior. Most of the previous sleep research has beenfocused on the neural processes occurring in the brain during sleep. However,complementary Autonomic Nervous System (ANS) fluctuations have been recordedacross sleep stages (NREM and REM) (Cellini *et al*., 2016; Whitehurst et al., 2016). Mostof what we know is correlational, warranting the need to understand the causal effect ofANS on sleep. One key pathway through which the ANS modulates sleep is *via* the vagusnerve. Transcutaneous vagal nerve stimulation (tVNS) is a novel, non-invasive, techniquethat can be used during sleep to target the vagus nerve. Usage of tVNS has been mostlylimited to studies conducted during the wake. Studies examining the impact of tVNS onsleep in healthy adults are scarce. The main aim of this project is to examine the impactof tVNS on sleep architecture.The Institutional Review Board of the University of Kentucky approved all experimentalprocedures. 36 young (aged 18-65; 18M,18F), healthy participants engaged in a two-week, within-subject sham-controlled and counterbalanced study, spending two nights inthe sleep lab. Each participant slept with polysomnography, and stimulation conditionswere counterbalanced across the two visits. Polysomnography was monitored in real timeand tVNS stimulation (active or sham) began once NREM Stage 2 onset was detectedand continued for ninety minutes. Paired t-tests were used to compare the means of sleeparchitectural variables across the active and sham tVNS conditions within the sameparticipants. Additionally, Pearson's correlation assessed the bivariate associationsbetween the stimulation intensity and the sleep architectural variables.We did not find any significant differences in the sleep architectural changes across theactive and sham nights. Interestingly, participants with higher stimulation intensityexhibited reduced NREM Stage 3 minutes ($r=-0.324$; $p=0.05$), and increased NREMStage 2 percentage ($r=-0.377$; $p<0.05$). Additionally, participants with higher stimulationintensity also showed increased wake minutes ($r=-0.367$; $p<0.05$) in the second quartile.The results showcase the nuanced effect of tVNS on sleep architecture. Future directionsinclude assessing EEG spectral components during tVNS active and sham nights.

Disclosures: A. Subramoniam: None. **G. Gilmore:** None. **L. Whitehurst:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

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Topic: F.07. Biological Rhythms and Sleep

Support: U.S. Department of Defense Grant W911NF1910280
NIH Grant NINDS-R01NS131389 (CC, GT).

Title: Inducing off periods during wakefulness reduces sleep pressure

Authors: *K. DRIESSEN, F. SQUARCIO, G. TONONI, C. CIRELLI;
Univ. of Wisconsin - Madison, Madison, WI

Abstract: Cortical neurons fire tonically during wake and become bistable in non-rapid eye movement (NREM) sleep, alternating between wake-like neuronal firing (ON/UP periods) and hyperpolarized silence (OFF/DOWN periods) once or twice per second. When ON/OFF alternations occur near-synchronously, the electroencephalogram (EEG) records slow waves in the 0.1-to 4.5 Hz range (slow wave activity: SWA). SWA reflects sleep need: it is high in early sleep after long wakefulness and decreases over the course of sleep. Correspondingly, OFF periods decrease in duration during sleep. This homeostatic behavior suggests that OFF periods may be related to the homeostatic functions of sleep. If so, the local induction of OFF periods during wakefulness should reduce homeostatic pressure in subsequent sleep. We optogenetically induced NREM-like OFF periods in local populations of excitatory neurons of the mouse cortex during active wakefulness, during the final 30-45 minutes of a 5-hour sleep deprivation (n = 7 adult male mice). We used both direct inhibition via the pan-neuronal expression of an anion-specific channelrhodopsin, as well as indirect inhibition of nearly all cortical neurons via a cation-specific (excitatory) channelrhodopsin expressed in somatostatin-positive GABAergic interneurons. In both models, the induction of OFF periods in a local network during wakefulness reduced SWA in that network during subsequent recovery sleep, and not in other cortical networks. In additional experiments (n = 10 adult male mice), mice underwent the same OFF period induction protocol, but were not allowed to enter recovery sleep and were sacrificed for quantitative immunoblotting-based measurement of synaptic phosphorylated AMPA receptor expression (pGluA1(845)), as natural sleep is known to reduce cortical synaptic pGluA1(845) expression. In both optogenetic models, the induction of OFF periods during wakefulness reduced synaptic pGluA1(845) expression specifically in the cortical networks where OFF periods were locally induced. In other experiments targeting the same networks of the same animals, we optogenetically enforced a constant, large tonic reduction in firing rate during active wakefulness. This manipulation caused a greater decrease in firing rate than the induction of NREM-like ON/OFF firing patterns, but had little or no effect on SWA in subsequent recovery sleep. Thus, OFF periods induced during active wakefulness can at least partially substitute for those occurring naturally during sleep and may promote a similar homeostatic function.

Moreover, such function is unlikely to be solely a ‘metabolic rest’ from tonic firing during wakefulness.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

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Topic: F.07. Biological Rhythms and Sleep

Support: NINDS R01 NS131821
NIMH F31MH132287-01A1
Kavli Neuroscience Award

Title: Dopamine signaling during NREM sleep is experience-dependent and promotes motor memory consolidation

Authors: *B. A. SULAMAN[1], E. CHEN[1], G. ROTHSCHILD[2], A. EBAN-ROTHSCHILD[3]; [2]Dept. of Psychology, [1]Univ. of Michigan, Ann Arbor, MI; [3]Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Dopaminergic (DA) signaling plays a central role in the modulation of various behaviors and physiological processes that are critical for survival, including feeding, movement, learning, motivation and arousal. A central DA population implicated in the aforementioned processes resides in the ventral tegmental area (VTA). While much is known about the experience- and state-dependence of VTA-DA neuronal activity, as well as the synaptic and behavioral consequences of dopamine release, during wakefulness, far less is known about these processes during sleep. Our research aims to fill this knowledge gap. We hypothesize that activity of VTA-DA neurons during sleep is experience-dependent and contributes to the consolidation of salient experiences. To test our hypothesis, we recorded activity from VTA-DA neurons, as well as dopamine release at major output regions, using fiber photometry during experiences of positive and negative valence and subsequent sleep. We found that salient positive, but not negative, experiences increase population activity of VTA-DA neurons during non-rapid eye movement (NREM) sleep. We also utilized chemogenetic and optogenetic approaches to investigate the necessity of VTA-DA neuronal activity during NREM sleep to memory consolidation. Our results suggest that VTA-DA neuronal activity during NREM sleep is critical for the consolidation of motor memories. Finally, to investigate potential mechanisms of dopamine-dependent memory consolidation, we are characterizing temporal relationships between VTA-DA neuronal activity and memory-related oscillatory activity during sleep. By revealing the dynamics and functions of DA signaling during sleep, our study will expand current understanding of a major neuromodulatory system critically implicated in flexible behavioral responses.

Disclosures: B.A. Sulaman: None. **E. Chen:** None. **G. Rothschild:** None. **A. Eban-Rothschild:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

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Program #/Poster #: PSTR354.09/K34

Topic: F.07. Biological Rhythms and Sleep

Title: Hypothalamic melanin-concentrating hormone neurons serving as a pacemaker drive deep sleep

Authors: *Y. ZHAO[1], Y. ZHAO[2], C. WANG[1], N. N. GUAN[1], C.-X. HUANG[1], J. SONG[1]; [1]Sch. of Med., Tongji Univ., Shanghai, China; [2]Sch. of Med., Tongji university, Shanghai, China

Abstract: To have enough deep sleep during night is essential for relieving sleep pressure. and maintaining wellbeing. In human adults, a stable monophasic sleep is characterized by the NREM/REM cyclic pattern with very occasional awakenings during the night. In the early stage of sleep, there is prolonged NREM sleep, termed N3 and identified as the deep sleep stages to allow the body quickly acquire the urgent needs. However, birds, zebrafish and some small mammals exhibit shallower multiphasic nature sleep pattern with short sleep cycles fragmented by frequent awakenings to avoid predation or dangers. Thus, it remains unclear whether the deep sleep pattern is an evolutional characteristic only belongs to human being or it could also apply to other species. The neural representation and mechanism underling such a deep-sleep pattern remain elusive. In this study, we reported a discrete deep-sleep pattern in zebrafish that is defined by prolonged sleep bout length, shorten wake duration and reduced bout numbers among the first hour following sleep deprivation. The same deep sleep pattern was also found in mice and characterized by the largely prolonged sleep cycle with multiple prolonged NREM stages with intermitted REM after sleep deprivation or nighttime physical exercise. The whole brain calcium imaging revealed the neural signature of such a deep sleep activity, characterized by global slow neuronal oscillations originally initiated from hypothalamus and propagating across multiple brain regions. Furthermore, the hypothalamic melanin-concentrating hormone (MCH) neurons was demonstrated as the pacemaker neurons which drives the deep sleep pattern in both zebrafish and mice. In general, these results provide evidence of a deep-sleep pattern evolutionarily conserved in both zebrafish and mice. We further revealed an essential role of MCH neurons in homeostatic control of deep sleep under high sleep pressure.

Disclosures: Y. Zhao: None. **Y. Zhao:** None. **C. Wang:** None. **N.N. Guan:** None. **C. Huang:** None. **J. Song:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

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Program #/Poster #: PSTR354.10/L1

Topic: F.07. Biological Rhythms and Sleep

Support: Innovationsfonden 2052-00054A

Title: Time-dependent fluctuations of hypothalamic histamine levels in mice

Authors: *C. G. HVIID[1,2], K. F. HERRIK[1], G. SØRENSEN[1];
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Abstract: Histamine (HA) plays a crucial role in the regulation of wakefulness and sleep. However, the timing of this regulation and the underlying mechanism remains elusive. This study provides insights of the time-wise interpretation of HA data and its correlation to sleep/wake cycles. We evaluated HA fluctuations during the active and inactive phases in male wild-type C57BL/6 mice. HA levels were quantified from the lateral hypothalamus every 10 or 20 minutes using microdialysis and LC-MS. Experiments began at either ZT0 (Lights on) or ZT12 (Lights off). After a 3-hour period of no interference, samples were collected from ZT3-ZT7 or ZT15-ZT19. Additionally, as a pilot experiment, we measured HA fluctuations in another wild-type mouse using fiber photometry (GRAB-HA1h sensor) alongside EEG and video. We found that mice during the dark phase generally have higher levels of HA across the 4 hours compared to light phase by visually inspecting each animal and calculating area under the curve. We detected fluctuations in the HA levels with 20-minute sampling rates only in few outliers. We detected fluctuations in HA with 10-minute sampling rates in microdialysis and confirmed the same changes with the GRAB-HA1h sensor recorded at 50Hz. Furthermore, based on the pilot data HA fluctuates in cycles that correlate with wake and sleep. Our study reveals the limitations of microdialysis measurements in 20-minute intervals due to the time-dependent fluctuations of HA levels. Hence, based on this, it will be beneficial to increase the recording frequencies used for measuring HA levels in vivo. In future studies, it would be interesting to look at narcoleptic mouse models that are hypothesized to have altered histaminergic system due to lack of orexinergic input. These findings highlight the importance of careful time-wise interpretation of HA data in sleep/wake research.

Disclosures: C.G. Hviid: None. **K.F. Herrik:** None. **G. Sørensen:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

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Program #/Poster #: PSTR354.11/L2

Topic: F.07. Biological Rhythms and Sleep

Support: U.S. Army Medical Research and Q14 Development Command, grant number A2-8357

Title: Comparison of spectral and visual sleep scoring of publicly available sleep databases

Authors: *J. A. ONTON;
UC San Diego, La Jolla, CA

Abstract: Visual sleep scoring has long enjoyed the status of sleep staging "ground truth". Commercially available automated algorithms come just as close to visual scorers as another human scorer, yet they only claim to facilitate visual scoring. This is because in order to validate the algorithm's accuracy, a human still needs to scroll through the entire data set as they would to score it alone. Additionally, visual sleep scoring was developed before modern computational tools that provide more nuanced information about the data that may be difficult for the human eye to perceive. In this study, we examine a spectral scoring technique that does not attempt to recapitulate visual scoring, but rather allows the spectral features of the whole night spectrogram to dictate the relevant stages. Using this method, it was clear that slow wave sleep consists of two regimes, one that dominates in the 0-1 Hz range, and the other in the 1-3 Hz range. It also showed that rapid eye movement (REM) sleep can be differentiated by beta power (~17-25 Hz), and gamma is an effective indicator of Wake. Using these features, a spectral scoring algorithm was created to classify 30s sleep epochs into Hi Deep, Lo Deep, Light, REM or Wake. This report shows how these stages map on to the currently understood visual scoring stages to facilitate a move toward spectral scoring, which takes a fraction of the time and effort, and is easily validated by comparison with the whole night spectrogram. Seven publicly available databases were used that included professional visual scoring results and either channel F3 or C3/4 for spectral scoring. Our results show that, across seven databases, visual REM was recognized as spectral REM 80-96% of the time. Light sleep was mostly scored as N2 (61-89%), and N3 was generally scored as either Hi or Lo Deep sleep (86-95%). The correspondence between visual and spectral Wake hovered around 50%, with most substitutions being for REM, Light and N1/N2. It is assumed that N1 will pull accuracy from Wake since it is a transitional stage that does not exist in spectral scoring. In addition, visual scoring tends to bounce between wake and sleep during what spectral scoring considers a homogeneous continuous stage, which can be visually detected in the whole night spectrogram. Finally, while spectral scoring is optimized for frontal channels which show the strongest slow oscillations and can be easily accessed on the forehead, channels across the scalp show generally similar patterns and return comparable spectral scoring hypnograms between F3, C3 and O1 (65-75%). Spectral scoring holds rich potential for fast, inexpensive, consistent, and easily validated sleep analysis.

Disclosures: J.A. Onton: F. Consulting Fees (e.g., advisory boards); CGX Inc.

Poster

PSTR354: Systems and Circuit Studies of Sleep

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.12/L3

Topic: F.07. Biological Rhythms and Sleep

Support: T32 MH064913
R01 NS112252

Title: Examining switching rates of resting state networks across arousal levels

Authors: *K. ROGGE-OBANDO[1,2], S. WANG[3], H. POURMOTABBED[3], C. MARTIN[4], S. GOODALE[3], Y. LI[5], J. HARDING[6], L. Q. UDDIN[7], M. RUBINOV[3], C. CHANG[8];
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Abstract: Changes in cognitive performance are related to arousal state. However, the brain-network interactions that support arousal-dependent cognitive changes have not been fully elucidated. One measure that has been associated with cognitive performance is network switching, a dynamic measurement of how frequently a brain network transitions between functional network communities. Interestingly, fatigue and sleep duration have been shown to influence network switching. However, to our knowledge, a direct comparison of the switching rates of resting-state networks between arousal states has not been carried out. Here, we investigate the network switching properties of three major brain networks (default-mode, salience, and central executive networks) across arousal states. According to the "triple network model", the salience network mediates switches between activation of central executive and default mode networks. In this study we use simultaneous EEG and fMRI data acquired from 19 subjects during resting state. Resting-state networks were derived using two complementary approaches: (1) group-level ICA, and (2) the FINDLAB atlas. We closely followed the methods presented in Pedersen et al., 2018 to determine the switching rate of each network across a scan. To determine the arousal state of each scan, we used Vigilance Algorithm Leipzig (VIGALL). We then calculated the effect size of the difference in network switching rate across arousal states. Next, we calculated a *p*-value for each network with three distinct null models. Each null model was constructed by altering each scan's timeseries and recomputing switching rate with these null data, aiming to test the extent to which the empirical finding depends on the properties of the timeseries that are perturbed in a given null model. For null model 1, each network's timeseries were randomized within a scan. Null model 2 recomputed a new timeseries that preserved the global signal from the original scan. Null model 3 recomputed the new timeseries while preserving each network's temporal variation values. The ICA-derived networks that showed significant arousal-dependent switching rates compared to at least one of the three null models were the dorsal-default mode network (DDMN; Cohen's d=0.89) and left central executive network (LCEN; Cohen's d=0.96). Interestingly, DDMN was the only significant network found when using the atlas-based networks to derive network time-series (DDMN; Cohen's d=1.16). These findings provide key insights into changes in network dynamics across different states of arousal, suggesting that DDMN dynamics in particular are robustly associated with low arousal.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.13/L4

Topic: F.07. Biological Rhythms and Sleep

Support: NIH P50HD103557
UCLA Chancellor's Research Fund

Title: Scheduled feeding improves behavioral outcomes and reduces inflammation in a mouse model of Fragile X syndrome.

Authors: *C. COLWELL[1], H.-B. WANG[2], K. NGUYEN-NGO[3], N. SMALE[4], C. A. GHIANI[5]; [1]Psychiatry, Univ. of California - Los Angeles, Los Angeles, CA; [2]Dept. of Psychiatry and Biobehavioral Sci., UCLA, Los Angeles, CA; [3]UCLA, Los Angeles, CA; [4]NYU Grossman Sch. of Med., New York, NY; [5]Pathology, UCLA, Los Angeles, CA

Abstract: Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by the abnormal expansion of CGG repeats in the fragile X mental retardation 1 (*Fmr1*) gene. Sleep disruptions are experienced by many FXS patients and we sought to explore these symptoms along with the possible benefits of a scheduled feeding intervention using the *Fmr1* KO model of FXS. We found clear evidence for sleep and circadian disturbances in the *Fmr1* KO mouse model including delay in the onset of sleep, fragmented rhythms with increases in cycle to cycle variability. The mutants exhibited clear deficits in their circadian behavioral response to light with reduced masking, light-induced phase shifts, resetting to 6 hr shifts in the LD cycle, and light-induced cFos expression in the suprachiasmatic nucleus. Interestingly, disruptions in social and repetitive behavior were correlated with sleep duration and fragmentation. In the attempt to improve the rhythms, we applied a feeding schedule (6-h feeding/18-h fast cycle) as a circadian-based strategy that boasts circadian rhythms independently of light. We found that this intervention significantly improved activity and sleep in the mutants. Strikingly, the feeding schedule also reduced repetitive behavior and increase social interactions in the Fmr1 KO mice. Finally, the feeding schedule reduced the elevated levels of Interferon-gamma and Interleukin-12 in the *Fmr1* KO mutants, suggesting that scheduled feeding may be an effective way to reduce inflammation. Together, our study points out that the *Fmr1* KO exhibit specific deficits in the light-input pathway to the circadian system and raises the possibility that these deficits may contribute to the sleep disruption that is so commonly experienced by FXS patients. The sleep disruptions were found to be correlated with the expression of ASD behavioral deficits in individual animals. Using the information that we gained about the deficits, we designed a

circadian-based intervention that improved behavioral outcomes and reduced the inflammatory signature of the *Fmr1* KO mice.

Disclosures: C. Colwell: None. **H. Wang:** None. **K. Nguyen-Ngo:** None. **N. Smale:** None. **C.A. Ghiani:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.14/L5

Topic: F.07. Biological Rhythms and Sleep

Support: JST Moonshot R&D (JPMJMS2012)

Title: A daytime nap accompanied by alleviation of sleepiness stabilizes brainwaves rhythms

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Abstract: The phenomenon of increased drowsiness in the afternoon, often observed due to the influence of the human circadian rhythm, can impair normal performance. To efficiently counteract this state, a 15-30-minute daytime nap, commonly known as a Power Nap, has been suggested. However, opinions regarding its effectiveness vary, with some reports indicating that drowsiness may not necessarily be alleviated. Here, to analyze the neurophysiological changes induced by a daytime nap, we compared differences in post-nap behavior and brain activity between cases where drowsiness improved and cases where it did not. Ten healthy adult males participated, undergoing three days of experimental sessions: two nap conditions and one control condition. In the nap condition (Nap), participants took a 20-minute daytime nap, with measurements of closed-eye resting-state electroencephalogram (EEG) and changes in tapping tasks evaluated before and after. In the control condition (NoNap), participants maintained a 20-minute period of wakeful rest instead of taking a nap. Participants were classified into two groups based on the results of questionnaires about their current subjective sleepiness and alertness levels (Stanford Sleepiness Scale): those experiencing improved drowsiness (Good) and those with unchanged drowsiness (Bad). First, we detected alpha oscillations in resting EEG data using an oscillation detection algorithm and calculated the proportion of alpha oscillations. The results indicated that the proportion of alpha oscillations during closed-eye resting state significantly increased in Nap-Good ($p=0.003$) and significantly decreased in NoNap-Bad ($p=0.009$). Moreover, a significant difference in the proportion of post-nap alpha oscillations was observed between Nap-Good and Nap-Bad ($p=0.013$). Second, we compared the duration and power of alpha oscillations between the post-nap periods of Nap-Good and Nap-Bad conditions. The results showed significant differences in both duration and power, with Nap-Good exhibiting longer durations and greater power of alpha oscillations compared to Nap-Bad (duration: $p < 0.001$, power: $p < 0.001$). These findings suggest the emergence of stable alpha

oscillations following a daytime nap accompanied by drowsiness relief. Considering that alpha oscillations reflect rhythmic bursting firing of hypothalamic-cortical neurons, these results imply stabilization of brain rhythmicity due to changes in hypothalamic activity.

Disclosures: R. Iwasawa: None. **S. Iwama:** None. **J. Ushiba:** A. Employment/Salary (full or part-time):; LIFESCAPES Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); LIFESCAPES Inc..

Poster

PSTR354: Systems and Circuit Studies of Sleep

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.15/L6

Topic: F.07. Biological Rhythms and Sleep

Title: Central sleep/wake-promoting nuclei contribute to the loss of responsiveness under isoflurane anesthesia in mice

Authors: L. JOYCE[1], R. NUTTALL[1], M. KREUZER[1], G. SCHNEIDER[1], ***T. FENZL**[2,3]; [1]Anesthesiol. and Intensive Care, Tech. Univ. Munich, Munich, Germany; [2]Tech. Univ. Munich, Klinikum rechts der Isar, Munich, Germany; [3]Anesthesiology and Intensive Care, Technical University Munich, Munich, Germany

Abstract: Introduction: Neural dynamics underlying loss of responsiveness (LOR), induced by general anesthesia (GA) are still poorly understood at the systemic level. Given the parallels observed between natural sleep and unconsciousness induced by anesthesia, it becomes imperative to understand and compare the neuronal mechanisms underlying these two physiological states. Here, we investigate whether sleep- and wake-promoting nuclei - controlling wakefulness (WAKE) and non-rapid eye movement sleep (NREMS) - show similar activities during LOR and recovery of responsiveness (ROR) under GA. This approach may help to describe the reversible shift from consciousness to unconsciousness at a systemic level. Methods: From 12 freely behaving male C57BL/6N mice (age: 12-14 weeks), local field potentials (LFP) were chronically recorded from the ventrolateral preoptic nucleus (VLPO), locus coeruleus (LC), and ventral posteromedial nucleus (VPM), together with chronic EEG recordings. After baseline EEG- and LFP-recordings (48h), GA was administered by increasing isoflurane concentration (0.1% every 2 minutes) until the first 5s of burst suppression were reached. Then, isoflurane concentration was reduced (0.1% every 2 minutes) until full responsiveness. EEG- and LFP-signals were constantly recorded for additional 48h. Next to the analysis of sleep/wake behavior, functional connectivity between VLPO and LC during NREMS, WAKE and GA was evaluated, applying coherence (CO) and Granger causality (GC) analyses. Results: Evaluation of LFP data (≤40 Hz) revealed a significant increase in CO between VLPO and LC during NREMS, as compared to WAKE. Analogous to the WAKE/NREMS transition, CO between the two nuclei increased after LOR, when compared to that before LOR. During

ROR, CO did not change significantly. The GC indices during WAKE and NREMS revealed that given the signal from VLPO, the predictability of the LC signal was higher. During NREMS, the GC index of VLPO predicting LC was significantly higher as compared to WAKE. GC indices between VLPO and LC during GA were found to be higher than that of NREMS or WAKE. GC indices before LOR, as compared to that after LOR revealed that the predictability of the VLPO signal was higher, given the signal from LC.
Discussion: Although their roles are not identical to those observed during NREMS and WAKE, VLPO and LC seem to participate in the process of inducing LOR under isoflurane anesthesia in mice. It remains unclear whether this is only passive as a consequence of LOR or active, serving as a prerequisite for LOR. Such parallels could not be extended to ROR, supporting the idea that ROR might not be a simple reverse mechanism of LOR.

Disclosures: L. Joyce: None. **R. Nuttall:** None. **M. Kreuzer:** None. **G. Schneider:** None. **T. Fenzl:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.16/L7

Topic: F.07. Biological Rhythms and Sleep

Support: JHU/APL Internal R&R

Title: Enhancing the clinical utility of polysomnography using self-supervised sleep foundation models

Authors: *W. G. COON, M. OGG;
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Abstract: Neural signals convey a wealth of information during sleep. This includes not only information about sleep depth and state, but also about health, wellness, illness, cognition, age, and other state/trait attributes of the sleeper. The current method of analyzing sleep—labeling overnight recordings of brain, eye movement, and muscle activity, in 30-second segments belonging to one of five sleep stages— discards enormous amounts of this information, which is a recognized drawback of what has become the de facto gold standard for sleep analysis. The recent availability of large repositories of sleep data, coupled with emerging breakthroughs in unsupervised AI, offers an opportunity to address this in principled, data-driven ways. Here we propose a method for discovering new information in sleep using self-supervised learning (a type of unsupervised machine learning that does not require human annotations) to build a foundation model (FM) that learns the latent structure of sleep from signals typically found in polysomnographic (PSG) sleep studies (i.e., brain, eye, and muscle activity; breathing; heart rate; and peripheral/autonomic indicators). The foundation model vastly accelerates learning multiple downstream tasks, providing the practical advantage that multiple applications can be derived

from the same FM. These include, for example, personalization of sleep analytics (e.g., age-, disease-, or person-specific sleep staging adjustments), estimation of "brain age" (a promising new biomarker of neurodegenerative disorders), and predicting cognitive and clinical states. Such techniques may bring the field closer to augmenting the current gold standard sleep staging system with more versatile, objective, and data-driven approaches.

Disclosures: W.G. Coon: None. **M. Ogg:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

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Program #/Poster #: PSTR354.17/L8

Topic: F.07. Biological Rhythms and Sleep

Support: NCT01273129
NCT04095026

Title: Neural synchrony measures across stages of consciousness

Authors: *R. VOLKMAN[1], J. I. CHAPETON[2], S. INATI[1], K. A. ZAGHLOUL[3];
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Abstract: Memory consolidation has been shown to occur during both awake and asleep states. However, the neural mechanism of memory consolidation is not fully understood. Prior work has found periods of bursting activity where neuronal firing shows temporal alignment across brain regions ("synchronous" states). These synchronous states are countered with periods of relatively unaligned neuronal firing ("asynchronous" states). The cognitive relevance of these synchronous vs. asynchronous periods is unknown, but we hypothesize that synchronous states may play a role in the mechanism of consolidating information into memory. To address synchronous states' role in cognition and memory, we analyzed the physiological conditions under which synchrony occurs. Using 24-hour intracranial EEG recordings and depth electrode single unit recordings from epileptic patients, we examined neural synchrony across stages of consciousness (awake, N3, and REM sleep). Here, we report our preliminary exploration, which analyzes synchrony across stages of consciousness through three measures. The first measure takes an average of synchrony values across each stage of consciousness to provide a stage average synchrony value. The second measure quantifies the duration of time spent in a synchronous state across each stage of consciousness. The third measure evaluates the percentage of time spent in a synchronous state within a given stage of consciousness by taking the duration of time spent in a synchronous state in a given stage over the total duration of time spent in that stage. These quantifications provide an initial framework under which further analysis may reveal the specific mechanism of how synchrony influences memory and cognition.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

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Program #/Poster #: PSTR354.18/L9

Topic: F.07. Biological Rhythms and Sleep

Support: Facultad de Medicina, UNAM

Title: Stress recovery, a function of sleep in crayfish

Authors: *J. HERNANDEZ-FALCON[1], K. MENDOZA-ANGELES[2], A. L. ARREDONDO[3]; [1]Physiol., Univ. Nacional Autónoma De México, Ciudad De Mexico, Mexico; [2]Fisiología, Univ. Nacional Autónoma de México, México, Mexico; [3]Physiol., Facultad de Medicina, UNAM, Ciudad de México, Mexico

Abstract: Sleep does not have a single proposed function, with memory consolidation being one of the most studied. Recovery from illness is an intuitive yet poorly studied function. Illness imposes a significant stress load on the individual and is associated with changes in sleep patterns. Stress is a demanding condition that mobilizes many functional resources of the individual, whether easily available or stored, in order to preserve life. In humans stressful conditions are associated, among others, with arterial hypertension and gut and sleep disorders, mainly gastritis and sleep disorders, respectively. Crayfish is an ideal biological model for studying sleep functions because this invertebrate shows similar sleep characteristics to those of vertebrates, but in a quite smaller and well-known brain. We exposed crayfish to two kinds of stress while measuring cardiac and respiratory activity, as well as sleep behavior. Stress conditions were mild, agonistic encounters for 45 minutes, or severe, hypoxia during 30 minutes. In both cases, we measured behavioral sleep duration during 4 consecutive hours after the stressful condition. Our results show that, besides the cardiac and respiratory adjustments during stress, sleep increased significantly after stress and lasted at least 2 days after the stronger stressor. These results imply that sleep fulfills a restorative function in crayfish.

Disclosures: J. Hernandez-Falcon: None. **K. Mendoza-Angeles:** None. **A.L. Arredondo:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

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Program #/Poster #: PSTR354.19/L10

Topic: F.07. Biological Rhythms and Sleep

Support: NIH grant No. AG068215
Lyman T. Johnson fellowship

Title: Investigation of EEG slow wave recovery following sleep disruption in a mouse model of Alzheimer's disease

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Abstract: Sleep plays an important role in maintaining brain function and cognitive health. However, in Alzheimer's disease (AD), this essential process is often compromised by sleep fragmentation (multiple interrupted bouts of sleep). These interruptions are not only symptoms but also exacerbate pathology and are associated with increased amyloid beta (Aß) accumulation in the brain. While the reduction of slow-wave sleep has been experimentally demonstrated to increase the deposition of Aß, the effects of interrupted sleep intervals on consolidation of slow-wave activity (SWA) remains unexplored. This IACUC-approved study utilizes electroencephalography (EEG) and electromyography (EMG) to investigate the effects of a sleep fragmentation (SF) protocol that mimics the sleep disruption frequently observed in AD patients, using 8-month-old male APP/PS1 knock-in mice that are genetically predisposed to amyloid plaque formation. Mice underwent surgery for the implantation of EEG/EMG headmounts, with bone screws positioned to sense cortical field potentials. After a 2-week recovery, a week of EEG recording was performed to establish baseline sleep patterns. In the next four weeks, SF was performed by gentle sensory stimulation, in a manner designed to mimic the pattern of disrupted sleep seen in AD. The protocol, performed Monday through Friday, involved one-hour-long blocks of sleep disruption at four different times of the 12-hour light phase separated by 90-minute undisturbed intervals. Following this intervention, EEG analysis was conducted. Particular attention was given to 0.5-2 Hz low delta power (LFP) in the EEG as a measure of SWA. Control mice were recorded alongside without sleep disruption. Preliminary EEG analysis of treated mice revealed surges in LDP immediately after the first two sleep disruption periods of the day compared to baseline levels, which suggests a homeostatic recovery of SWA during the expected sleep rebound. Interestingly, the surge in LDP is much reduced following the subsequent two blocks of sleep disruption later in the day, possibly due to adequate prior recovery of SWA or the approach of the inactive dark phase of the diurnal rhythm. In contrast, control mice showed no consistent trends in LDP or activity, further highlighting the large swings seen in the SF protocol. Further data collection is ongoing to investigate the significance of these observations.This study is expected to yield useful insight into whether slow wave activity is consolidated between periods of sleep disruption in an experimental SF protocol and the correlation with pathology in a widely used animal model of AD.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.20/L11

Topic: F.07. Biological Rhythms and Sleep

Support: NIH Grant DC004290
NIH Grant GM109086

Title: Similar neurophysiological changes between dexmedetomidine and sleep contrasted with propofol anesthesia using human intracranial recordings

Authors: *B. M. KRAUSE[1], E. R. DAPPEN[2], M. SUTHERLAND[1], R. N. MUELLER[3], H. KAWASAKI[4], K. V. NOURSKI[4], M. I. BANKS[1];
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Abstract: Dexmedetomidine (DEX) is an α2-adrenergic sedative and general anesthetic adjunct. DEX is thought to induce a more sleep-like sedated state (Nelson, L.E. et al 2003, Anesthesiology 98, 428-436) compared to general anesthetics like propofol. Previously, we showed that comparable cortical network reorganization, quantified as effective dimensionality (D_E) of functional connectivity matrices, occurs during propofol anesthesia and sleep. Delta band (1-4 Hz) power increases during sleep and some forms of anesthesia. Here, we compare average delta power and effective dimensionality in DEX-induced sedation and loss of responsiveness to sleep and propofol anesthesia. Research participants were neurosurgical patients with medically refractive epilepsy implanted with intracranial electrodes for clinical monitoring prior to surgical resection. Intracranial electroencephalography (iEEG) recordings were performed during task-free wakefulness (resting-state), overnight sleep, and during induction of anesthesia prior to resection. Overnight sleep recordings were staged based on EEG and EMG recordings via polysomnography. During induction experiments, awareness was monitored using the Observer's Assessment of Arousal/Sedation (OAA/S) scale. DEX or propofol was infused at gradually increasing dose until participants were unresponsive to command. Delta power decreased over time post-implant surgery in iEEG participants. Regression fit to resting-state recordings was used to adjust measurements of delta power, facilitating comparisons over days. D_E was calculated using the spectrum (eigenvalues) from diffusion map embedding applied to pairwise orthogonalized gamma (30-50 Hz) power envelope correlations (Krause, B.M. et al 2023, Cerebral Cortex 33, 9850-9866). D_E decreased during DEX and propofol-induced sedation and decreased further during loss of responsiveness. D_E also decreased with progressively deeper stages of non-REM sleep. Delta power increased progressively in deeper stages of non-REM sleep and also increased with sedation and loss of responsiveness during induction with DEX. However, delta power changes with propofol were smaller than for DEX or during sleep. The slope between changes in D_E and delta power was comparable between DEX induction and sleep, with unresponsiveness under DEX comparable to N2 sleep for both neurophysiological measures. These results are consistent with DEX inducing a more sleep-like change in

responsiveness. Given the high incidence of dreaming reported during N2 sleep and DEX anesthesia, these results suggest that delta power increases may indicate disconnection rather than unconsciousness.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

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Program #/Poster #: PSTR354.21/L12

Topic: F.07. Biological Rhythms and Sleep

Support: The Koerner Family Foundation New Scientist Program
The Krembil Foundation
Canadian Institutes of Health Research
Canadian Foundation for Innovation
CAMH Discovery Fund

Title: Longitudinal co-trajectories of neural dynamics underlying sleep and depression

Authors: *M. ABDELHACK, R. WICKRAMATUNGA, D. FELSKY;
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Abstract: Relationships between neural signatures of sleep and depression are complex with conflicting observations, such as depression being associated with both insomnia and hypersomnia, and sleep deprivation acting as an effective antidepressant. Previously, we found opposing functional neural associations between resting and task-engaged states, demonstrating a counterintuitive relationship: neural signatures of insomnia and depressive symptoms were associated with brain-wide hyperconnectivity at resting state, typical of those who actually received more hours of sleep per night measured by accelerometry. In the task condition, the opposite was true. This raises important questions of causation between insomnia, depression, and functional hyperconnectivity. In the present study, we begin to address this question by investigating temporal trajectories of these relationships with repeated fMRI scans paired with measures of sleep, depression, and cognition in a subset of the UK Biobank (N=1188). We measured the association between changes in fMRI measures between two scans (both task and resting state) and the change in phenotypes reported between each scan session. This revealed that resting-state brain-wide associations between change in frequency of insomnia and sleep duration were positively correlated ($r=0.216$; $p=0.0016$), similar to previous cross-sectional analyses. However, the same neural associations of change in depression symptoms and sleep duration were not significantly correlated. Additionally, in the task-based condition, we found brain-wide hypoconnectivity associated with change in insomnia frequency, mirroring cross-sectional results. Given that longitudinal data reproduced only the results from the cross sectional

analysis for insomnia, they support the notion of insomnia and not depression as a precursor for the hyperarousal state where neural dynamics resemble those of rested wakefulness. This also suggests a possible causal relationship between insomnia and functional brain changes which could subsequently lead to depressive symptoms. This data-driven hypothesis extracted from the general population could guide new trials in clinical populations and ultimately inform new and more effective diagnoses and interventions for both depression and insomnia.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.22/L13

Topic: F.07. Biological Rhythms and Sleep

Support: Scanlan Center for School Mental Health Research Grant

Title: Objective and longitudinal assessment of sleep quality, daily affect and social media use in adolescents: Implications for mental health

Authors: M. LOTT[1], S. C. KOESTERER[1], E. MACKELLAR[1], A. MCCLEERY[1], J. PLATT[2], G. BARDHOSHI[3], *B. BARAN[4];
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Abstract: Adolescence is a unique period of rapid changes in sleep physiology, circadian regulation of sleep/wake circuitry, personal autonomy and peer relations. Recent increases in youth mental illness occurred in parallel with an increase in social media use (SMU) and poor sleep health, suggesting they may play a role in the emergence and exacerbation of mental health problems in adolescents. The goal of the present study was to investigate the role of sleep on SMU, affect and mental health in adolescents. We hypothesized that objective measures of sleep disruption would predict mental health problems, and SMU would interfere with sleep quality. 50 adolescents (12-18 yrs old) were recruited from the community and participated in a 14-day assessment that included wrist actigraphy for accurate and non-invasive measure of sleep and wake habits, smart-phone app based ecological momentary assessments of daily mood, affect and SMU, and a clinical diagnostic interview. While data collection is ongoing, preliminary results are based on 16 participants who completed all assessments (14.4 ± 1.5 yrs, 10F/6M). On average, participants spent 126 (±118) mins interacting with social media every day. SMU correlated with increased night to night variability in sleep duration (r= .79, p<.001) and sleep efficiency (r= .58, p=.03). Internalizing symptoms correlated with reduced sleep efficiency (r= -.61, p=.015) and increased sleep fragmentation (r= .55, p=.03). Further, subjective ratings of daytime sleepiness correlated with self-reported mood symptom severity (r= .78, p<.001). We did not observe any differences in sleep quality between weekend and weekdays, or any relations

between SMU duration and mental health problems. Both objective and subjective measures of sleep quality predicted mood and internalizing problems in adolescents. We observed strong relations of SMU duration with sleep disruption but not mental health problems. This reflects that the social media environment is complex and dynamic, with features that are likely both beneficial and harmful for adolescent mental health. Data collection is ongoing and future analytical plans include elucidating the effects of day to day differences in SMU on night to night variability in sleep.

Disclosures: M. Lott: None. **S.C. Koesterer:** None. **E. MacKellar:** None. **A. McCleery:** None. **J. Platt:** None. **G. Bardhoshi:** None. **B. Baran:** None.

Poster

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Program #/Poster #: PSTR354.23/L14

Topic: F.07. Biological Rhythms and Sleep

Support: K01 MH114012
Iowa Neuroscience Institute, Neuroscience, Development and Mental Well-being Ideas Lab Award

Title: Non-rapid eye movement sleep oscillations, resting-state functional connectivity and mood symptoms in children with anxiety disorders

Authors: *H. ARPACI[1], A. RIVERA-DOMPENCIEL[2], A. TRIPATHY[3], I. BECIC[2], A. BARRY[2], V. MAGNOTTA[4,5], B. BARAN[1,5];
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Abstract: Anxiety disorders impact approximately one-third of the population, often manifesting during adolescence, a period marked by rapid changes in prefrontal cortex functional connectivity. Sleep disruptions precipitate clinical symptoms in anxious youth. Non-rapid eye movement (NREM) sleep oscillations, crucial for brain development, affect, and cognition, undergo significant maturational changes during puberty, aligning with cortical maturation. The primary aim of the present study was to investigate the effects of the integrity of NREM sleep oscillations on ventromedial prefrontal cortex (vmPFC) functional connectivity, anxiety, and mood symptoms. Forty-three participants (9-13 yrs, mean: 11.28 yrs, n(anxiety)=17, n(comparison)=26) completed a nocturnal polysomnography session (32-channel EEG acquisition) and, on a separate session, 7T resting-state functional connectivity study. NREM sleep spindles and slow oscillations were detected with validated automated algorithms. vmPFC functional connectivity was quantified using a seed-based approach. Symptom severity was quantified with Child Behavior Checklist (CBCL) and Revised Children's Anxiety and

Depression Scale (RCADS). Regressions between symptoms and NREM oscillation characteristics were based on 3 representative electrodes (Cz, Fz, Pz). Spindle duration was significantly reduced in children with anxiety (7 electrodes, tsum = -17.04, p-corrected = 0.04), and across the entire sample, predicted depressive mood such that shorter spindle duration was associated with increased depressive symptoms (frontal: p <0.001, central: p =0.03, parietal: p =0.02). There were no other group differences in NREM oscillations or sleep architecture. MRI data analysis is currently underway. In a predominantly prepubertal sample of children with anxiety disorders we observed a decrease in spindle duration compared to typically developing children, in the context of comparable sleep duration, quality, and architecture. This reduction in spindle duration was linked to depressive symptoms. A recent study on older adolescents at risk for psychotic disorders demonstrated a notable decrease in spindle duration. These findings imply that changes in spindle duration might serve as a marker for general psychopathology during adolescence. While analyses are underway, we hypothesize that the reduction in NREM sleep spindle duration will moderate the relations between vmPFC functional connectivity and emotion regulation, and mood deficits.

Disclosures: H. Arpaci: None. **A. Rivera-Dompenciel:** None. **A. Tripathy:** None. **I. Becic:** None. **A. Barry:** None. **V. Magnotta:** None. **B. Baran:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.24/L15

Topic: F.07. Biological Rhythms and Sleep

Support: Velux Pr. 1283

Title: Sleep-like slow waves interleave spontaneous smartphone behavior

Authors: *R. KOCK[1], D. HOF[1], W. WAN[1,2], R. HUBER[3], A. GHOSH[1];
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Abstract: During periods of wakefulness, the brain can exhibit slow oscillatory activity (1-4 Hz) resembling sleep slow waves. These slow waves may be confined to cortical areas as if in local sleep. On the one hand, slow waves may help sustain behavior by allocating rest periods to brain regions experiencing intense activity. On the other hand, their occurrence can disturb ongoing brain function. Here we show that slow waves commonly occur when engaged in real-world behavior, even in the absence of severe sleep deprivation. We recorded scalp EEG signals while people used their smartphones. We separated the diverse smartphone behaviors according to their temporal dynamics. Next, we addressed how the slow waves varied according to smartphone temporal dynamics. The slow waves were quantified according to their origin, duration, and spread. By using mass-univariate statistics and data-driven dimensionality

reduction we reveal the patterns linking the slow waves and smartphone behavior. These patterns help unravel how the slow waves are distributed to balance the benefits of local sleep and the brief loss of function.
Authors R.K. and D.H. contributed equally to this work.

Disclosures: R. Kock: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author R.K. is co-founder of Axite BV., Leiden, The Netherlands. Axite provides a telemonitoring solution for cognitive functions by linking consumer-grade EEG and smartphone behavior. **D. Hof:** None. **W. Wan:** None. **R. Huber:** None. **A. Ghosh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A.G. is a co-founder of QuantActions (QA), AG., Zurich, Switzerland. This company focuses on converting smartphone taps into mental health indicators. This study uses data collection services from QA,, A.G. is scientific advisor of Axite. B.V., This study is related to a patent filed by A.G..

Poster

PSTR354: Systems and Circuit Studies of Sleep

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.25/L16

Topic: F.07. Biological Rhythms and Sleep

Support: Alchemist Project 20012355

Title: Posterior connectivity with high accuracy in classifying conscious states using machine learning

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Abstract: Consciousness is maintained through intact communication between brain regions. Therefore, connectivity might discern the conscious states, although it has not been rigorously tested. Machine learning analysis is robust for classification demanding less a priori knowledge. Thus, we employed machine learning analysis to classify conscious states with functional connectivity between resting state networks (RSNs). We recruited 73 medically intractable epilepsy patients (38 males and 35 females; age: mean = 33.8, SD = 10.8 years) with intracranial electroencephalography (iEEG) monitoring. The iEEG data both in the conscious state and in the unconscious state under general anesthesia were recorded. General anesthesia was achieved via a target-controlled infusion of propofol and remifentanil. We estimated functional connectivity using the amplitude envelope correlation (AEC) and the weighted phase lag index (wPLI) across frequency bands from delta to high gamma. We converted the connectivity between all electrode

pairs into connectivity between resting state networks (RSNs) based on a 7-network parcellation. We employed a support vector machine (SVM) with a radial basis function kernel. Each SVM classifier was trained using the connectivity values between RSNs across two states. We used a leave-one-subject-out cross-validation technique to ensure our model's generalizability and calculated the mean accuracy by averaging the accuracy scores from each cross-validation fold. Features were considered prominent if their z-scores were above 2 in the distribution of the classification models' accuracies.The classification accuracy, which was exhibited by z-scores above 2, was 77.8±2% (ranging from 75.7% to 82.9%). The connectivity in the visual network was the feature with the highest accuracy classifying the two conscious states. Among various band frequencies in the visual network, connectivity using AEC showed high classification accuracy within the delta and theta range, while that using wPLI was in the beta and low gamma range. Therefore, posterior connectivity is most dominant in classifying conscious states.

Disclosures: M. Choe: None. **S. Jin:** None. **J. Kwon:** None. **C. Chung:** None.

Poster

PSTR354: Systems and Circuit Studies of Sleep

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.26/L17

Topic: F.07. Biological Rhythms and Sleep

Support: NIH Grant R01 GM109086
NIH Grant R01 DC004290

Title: How does consciousness reboot? Tracking human single neuron activity during emergence from propofol anesthesia

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Abstract: Although much is known about the molecular and cellular effects of general anesthetics, the neural mechanisms underlying loss and recovery of consciousness during anesthesia remain elusive. Time to emergence from anesthesia is variable between patients and may influence postsurgical cognitive outcomes. During emergence, the brain appears to traverse metastable network states, but whether there is a consistent and specific spatiotemporal sequence of neuronal activity during emergence is unclear. Here, we examined the activity of single neurons in medial temporal, prefrontal, and parietal cortex while patients transitioned from propofol anesthesia to an awake, responsive state. Participants were adult neurosurgical patients with intracranial electrodes undergoing chronic monitoring for refractory epilepsy. Data were obtained immediately following electrode implantation as patients emerged from propofol

anesthesia. Single unit activity was recorded using Behnke-Fried microwire bundles that extend beyond the tip of the clinical recording electrodes. After research recordings had begun, propofol was continued for 5 minutes and then turned off. Muscle relaxants were fully reversed before propofol was stopped. Patients were monitored continuously for spontaneous movement and response to verbal commands. Single neurons were isolated offline and firing rates were examined over the entire time course of emergence from anesthesia, as well as within specific windows of interest after propofol cessation and behavioral response. Across all isolated neurons (n = 150; five patients), firing rates were 2.50 Hz at baseline (IQR: 3.14), 2.48 Hz immediately following propofol cessation (IQR: 2.89), 3.38 Hz prior to responses to command (RC; IQR: 3.35) and 3.82 Hz following RC (IRQ: 3.78). The earliest increases in activity occurred prior to overt RC and were observed in the hippocampus, amygdala and parahippocampal gyrus. Although the majority of neurons increased their activity prior to or following RC relative to baseline, others within the same brain regions demonstrated decreases, suggesting heterogeneity across the neuronal population. Intracranial recordings from single neurons during emergence from propofol anesthesia rev**ealed** heterogeneous activity, with most neurons in medial temporal regions showing increased firing before patients were responsive to verbal commands. Thus, brain activity in high order medial temporal regions may presage restoration of consciousness after anesthesia. To our knowledge, this is the first report of single neuron activity recorded in humans throughout emergence from general anesthesia.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

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Topic: F.07. Biological Rhythms and Sleep

Support: NIH Grant R01-GM109086
NIH Grant R01-DC04290
NIH Grant UL1-RR024979

Title: Changes in cortical slow wave activity during chronic invasive epilepsy monitoring

Authors: *E. R. DAPPEN[1], B. M. KRAUSE[2], M. I. BANKS[2], K. V. NOURSKI[1];
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Abstract: Cortical slow wave activity (SWA; delta band, 1-4 Hz) has long been considered a biomarker of altered states of consciousness, with increased SWA observed during anesthesia, sleep, coma, and delirium (Frohlich et al., Brain 2021;144:2257-77). SWA is not necessarily predictive of disordered consciousness. Elevated SWA has been observed in neurosurgical patients following intracranial electroencephalographic electrode implantation for monitoring

seizures (Sachdev et al., J Neurophysiol 2015;114:1248-54). The current work sought to characterize the time course of elevated SWA following electrode implantation and examine contributions of patient demographics, type and duration of surgery, and duration of emergence from general anesthesia. Participants were adult neurosurgical patients implanted with intracranial electrodes (either a combination of subdural and depth arrays or depth arrays alone) for clinical monitoring of their epilepsy. Resting state cortical activity was recorded at multiple time points, including early (<48 hrs.) and late (>120 hrs.) post-operative period, typically up to 14 days. Data analysis of cortical activity in the delta (1-4 Hz) and beta (14-30 Hz) frequency bands was conducted using a linear mixed effects modeling approach to account for between-participant heterogeneity. SWA decreased throughout the monitoring period with a similar time course in temporal, frontal, parietal and occipital regions, suggesting a global phenomenon. By contrast, beta power remained stable over the course of monitoring. Electrode implantation requiring a craniotomy for placement of subdural arrays was associated with higher SWA that underwent a steeper decline during monitoring compared to cases without craniotomy (i.e., when only depth electrodes were implanted). In craniotomy cases, recordings from depth electrodes yielded higher SWA and lower beta power than subdural electrodes. No consistent differences in SWA were observed when considering age, sex, surgery duration, anesthesia emergence duration, type of recording system, or recording environment (operating room or clinical research unit). The results are consistent with a post-operative increase in SWA that resolves over the course of monitoring period. Post-operative changes in SWA are related to the type of surgery and the type of electrodes used.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.28/L19

Topic: F.07. Biological Rhythms and Sleep

Support: MH110274

Title: Associations between sleep and hippocampal subfield surface area development in infants aged 0-27 months

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Abstract: Background: The connections between sleep and memory consolidation is well-established, with the hippocampus playing a central role. In early infancy, sleep patterns mature—daytime sleep decreases, nighttime sleep extends, and awakenings in the night reduce—while the hippocampus undergoes rapid development. Despite these parallel changes, the potential association between sleep pattern maturation and hippocampal development in infancy remain largely unexplored, primarily due to the lack of analysis tools for extracting hippocampal structural phenotypes during early infancy. Here we explored their associations in infants aged 0-27 months. **Method**: A total of 158 infants (17.66 ± 12.66 months) and 307 T1-weighted MRI scans were included in this study. Sleep was assessed using the Brief Infant Sleep Questionnaire, which measures sleep onset problems, quantity and quality. We applied Non-negative matrix factorization to delineate developmentally distinct hippocampal regions based on the surface area (SA) trajectories, and through which categorized these regions into the hippocampal subfields, including head, body, and tail. General additive models were used to control for age effects for both sleep and hippocampal metrics. We first explored the overall relationship between sleep metrics and hippocampal subfield SA across all ages using linear mixed-effect models. We then stratified subjects into four age groups (0-6, 6-12, 12-18, and 18-27 months), reflecting key developmental stages of the hippocampus. Subsequently, linear mixed-effect models were used to assess concurrent associations within each group while linear regression models to explore longitudinal relationships between sleep metrics and hippocampal subfield SA. FDR corrected for multiple comparisons. **Results**: No significant associations were found in the overall sample. However, age-specific analyses showed varying relationships among different age periods. For 0-6 month-olds, night waking frequency negatively correlated with hippocampal body SA at 6-12 months (β= -53.08, adjusted p = 0.024). No significant associations were found in the 6-12-month-olds. For 12-18 month-olds, sleep onset latency positively correlated with hippocampal tail SA both concurrently (β = 33.08, adjusted p = 0.003) and at 18-27 months (β = 52.98, adjusted p = 0.008). **Conclusion**: The hippocampal body and tail have been implicated associated with memory consolidation. Our findings revealed age specific associations between infant sleep and hippocampal body and tail SA, offering evidence linking sleep matrices with hippocampal subfield development during infancy.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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Topic: F.07. Biological Rhythms and Sleep

Support: NIH Grant R01-DC04290
NIH Grant R01-GM109086
NIH Grant UL1-RR024979

Title: Modulation of auditory novelty processing by dexmedetomidine and natural sleep: A human intracranial electrophysiology study

Authors: *K. V. NOURSKI[1], M. STEINSCHNEIDER[1], A. E. RHONE[1], R. MUELLER[1], M. I. BANKS[2];
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Abstract: Suppression of neural activity outside canonical auditory cortex associated with short-term auditory novelty (local deviance, LD) induced by propofol may represent a biomarker of loss of consciousness (Nourski et al., J Neurosci 2018, 38:8441-52). By contrast, long-term novelty (global deviance, GD) effects are abolished at subhypnotic doses of propofol. Unlike the GABAergic agent propofol, dexmedetomidine is an alpha-2 adrenergic agonist that induces sleep-like sedation. This study examined whether the changes in auditory novelty processing could be generalized to dexmedetomidine and sleep. Intracranial recordings were obtained in neurosurgical patients undergoing monitoring for refractory epilepsy. Stimuli were vowel sequences incorporating within- and across-sequence deviants (LD and GD, respectively). Dexmedetomidine infusion was titrated to reach sedation with responsiveness to command and then to loss of responsiveness (LOR). Neural activity was examined in auditory cortex and other brain regions. Averaged evoked potential (AEP) and high gamma (70-150 Hz) band power were used to assess cortical activity elicited by the stimuli. AEP LD/GD effects were more broadly distributed compared to high gamma novelty effects in the awake state. The effects of dexmedetomidine were consistent with those previously observed with propofol: subhypnotic doses led to decreased LD effects in medial temporal and prefrontal cortex and caused a near-complete loss of GD effects. LOR was associated with loss of LD effects in prefrontal cortex and the temporal lobe beyond auditory cortex. LD effects within canonical auditory cortex were preserved following LOR. LD and GD effects during daytime sleep were similar to those observed with dexmedetomidine with the exception of a greater reduction in LD effects within lateral superior temporal gyrus during sleep. Results support the generalizability of changes in cortical sensory processing from propofol to dexmedetomidine and sleep. LD effects outside canonical auditory cortex may represent a biomarker of conscious auditory novelty processing. Variable reduction in LD effects indicates that disruption of sensory processing following loss of consciousness may not follow identical trajectories, warranting a more nuanced description of circuit disruption.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.30/L21

Topic: F.07. Biological Rhythms and Sleep

Support: Intramural Research Program of the NIH, NINDS

Title: Increased Intra-Thalamic Functional Connections from Wake to NREM sleep and NREM to REM sleep: Insights from a Two-Night EEG-fMRI Study

Authors: *N. YANG[1], D. PICCHIONI[2], J. DE ZWART[3], Y. WANG[4,1], J. ZHOU[4], P. VAN GELDEREN[4], J. H. DUYN[5];
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Abstract: Human beings spend about a third of their lives sleeping, yet our understanding of sleep and its functions remains limited. Sleep is characterized by distinct stages, classified by polysomnography (PSG), which combines electroencephalography (EEG) measures of brain activity with several physiological measures. These stages include N1, N2, and N3 non-rapid eye movement (NREM) stages, as well as the REM stage. However, PSG has limitations in tracking brain activity, especially in subcortical regions. Combining PSG/EEG with fMRI can provide insights into subcortical activity changes across sleep stages. Twelve healthy young volunteers (age 24 ± 3.5, 8 females) participated in this in-scanner sleep study for two consecutive nights (about eight hours each night). The first night served as an adaptation night. All participants reached REM sleep on the second night. After standard data preprocessing, including global signal regression, fMRI time courses from voxels were averaged within each of the 36 subcortical regions of interest (ROIs) from the Seitzman 300-ROI brain atlas. The fMRI data were then segmented into epochs (longer than 30 TRs, TR = 3s) corresponding to each sleep stage. Dynamic functional connectivity (FC) was computed as Fisher-transformed correlation coefficients on these epochs using a sliding window method (window length = 30 TRs, step = 1 TR). We found that on the second night, the average FC between each pair of the 12 thalamic ROIs (intra-thalamic FC) increased linearly from wakefulness (0.24) to N1 (0.36), N2 (0.41), N3 (0.48), and REM (0.66) stages. This trend was also observed on the first night, despite having fewer REM and N3 epochs, and was independent of global signal regression. These findings underscore the stage-specific nature of functional thalamic relationships across the wake/NREM/REM/wake cycle, suggesting a need for future studies to focus on thalamic functions in understanding sleep transitions and cycling.

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Poster

PSTR354: Systems and Circuit Studies of Sleep

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR354.31/L22

Topic: H.04. Executive Functions

Support: NIH NS098981

Title: Thalamocortical profile of propofol-induced loss of consciousness and wakefulness in the human brain

Authors: *E. MURPHY[1], M. J. MCCARTY[2], J. SAVARRAJ[3], J. LI[4], N. TANDON[5]; [1]Univ. of Texas Hlth. Sci. Ctr., Houston, TX; [2]Neurosci., MD Anderson UT Hlth. Grad. Sch., Houston, TX; [3]Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [4]Rice University/ UT Hlth. Houston, Houston, TX; [5]Neurolog. Surgery, McGovern Med. Sch. at UT Hlth., Houston, TX

Abstract: The spatiotemporal neural dynamics of the loss of consciousness (LOC) and the regaining of consciousness are yet to be fully characterized in humans. Previous research has been cortico-centric in its focus, and has not explored multiple types of consciousness state transitions within-subjects. It is increasingly common to consider the role of subcortex in the types of cortico-cortical dynamics thought to underlie consciousness. Consequently, we monitored anesthesia-induced LOC (n = 5), waking from an anesthetized state (n = 29), and LOC through natural sleep (n = 4), in a large cohort of epilepsy patients with intracranial stereotactically placed depth electrodes (sEEG), a Medtronic deep brain stimulation Percept device, or a NeuroPace responsive neurostimulation (RNS) device within the thalamus. Four subjects underwent all three of these transitions in consciounsess, and had simultaneous electrode coverage across frontotemporal cortices and at least two thalamic nuclei (anterior nucleus, ventral lateral nucleus, centromedian nucleus, pulvinar). We detailed spectral characteristics within different parcellations of thalamic nuclei between wakefulness and LOC. We charted low-frequency power changes, high gamma power changes, phase-amplitude coupling (PAC) modulations, and signal complexity (via Lempel-Ziv compressibility; LZC) dynamics throughout stages of gaining or losing consciousness. We found that both the anterior and centromedian thalamic nuclei exhibit later low-frequency and LZC decreases than cortical sites (with the exception of anterior insula) during propofol-induced LOC, remaining at pre-induction baseline activity until after LOC. We discovered increased alpha-gamma PAC between anterior and centromedian thalamic nulcei and frontotemporal cortical electrodes after LOC relative to wakefulness. During waking from anesthesia, anterior thalamic nucleus and pulvinar provided more robust and reliable low-frequency signatures of consciousness, relative to other nuclei, with anterior regions being dominated by beta power increases during wakefulness and pulvinar regions being dominated by low-frequency (2-15Hz) decreases. We also charted comprehensive thalamocortical interactions during natural sleep. In general, LZC decreases occurred earlier than low frequency power decreases and were found to be closer to the behaviorally-marked point of LOC, suggesting that this measure may be a more accurate biomarker of LOC than power fluctuations.

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Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.01/L23

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: JST FOREST JPMJFR205M
JSPS KAKENHI 19H03994
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JSPS KAKENHI 20K20619

Title: Lactate signaling in the ventromedial hypothalamus suppresses noradrenaline release linked to whole-body fat oxidation during endurance exercise: A role for GPR81 in fatigue development

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Abstract: Although fatigue during exercise serves as a crucial biological defense mechanism to prevent overexertion, its neurobiological mechanisms remain largely unknown. The ventromedial hypothalamus (VMH), a center of energy metabolism, plays an important role in endurance exercise by enhancing whole-body fat oxidation. We recently found that endurance exercise increases brain lactate derived from glycogen, a glucose storage molecule in astrocytes, through noradrenergic activation. Brain lactate is a crucial energy source for active neurons but serves as an inhibitory signal for cAMP synthesis, which activates noradrenaline release in neurons, via a lactate receptor (GPR81) expressed mainly at synapses. We thus hypothesized that lactate significantly increases in the VMH during endurance exercise and suppresses noradrenaline release and whole-body fat oxidation via GPR81, which serves as a fatigue development mechanism via a negative feedback system. To test this hypothesis, we first conducted metabolomics on the hypothalamus of rats exercised to exhaustion. Metabolomics revealed that exhaustive exercise resulted in elevated lactate concentrations without altering ATP levels in the hypothalamus, suggesting a potential protective role of lactate in maintaining ATP levels. Next, we examined the effect of GPR81 signaling on whole-body fat oxidation during endurance exercise. Wistar rats were injected with 4-CIN (monocarboxylate transporter 2 inhibitor) or 3, 5-DHBA (GPR81 agonist) into the VMH, and performed 30 minutes of moderate-intensity exercise (20 m/min) in a treadmill metabolic chamber. O_2 consumption (VO_2), CO_2 emissions (VCO_2), and respiratory exchange ratio (RER) were measured as indices of whole-body fat metabolism. The 4-CIN injection did not affect VO2 but increased both VCO2 and RER during endurance exercise. Similarly, 3,5-DHBA did not change VO2 but increased both VCO2 and RER, indicating that lactate acts as an inhibitory signal for whole-body fat oxidation through GPR81. Finally, we assessed the effect of GPR81 signaling on noradrenaline release in the VMH during endurance exercise using microdialysis. 4-CIN increased extracellular lactate levels and diminished noradrenaline release, whereas 3,5-DHBA reduced both extracellular lactate and noradrenaline release in the VMH. These results clearly suggest that VMH lactate signaling via GPR81 suppresses noradrenaline release linked to whole-body fat oxidation during endurance exercise, repositioning lactate as a novel gliotransmitter in shaping exercise-induced fatigue as a brain defense mechanism.

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Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

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Program #/Poster #: PSTR355.02/L24

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: R01NS123023
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Title: Mice carrying a novel NAMPT mutation exhibit metabolic impairments

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Univ. of Missouri, Columbia, MO

Abstract: Nicotinamide adenine dinucleotide (NAD^+) is one of the most abundant metabolites in the body and is critical for many cellular processes including glycolysis, oxidative phosphorylation, and DNA repair. In mammals, the majority of NAD^+ is produced intracellularly via the NAD^+ salvage pathway, where nicotinamide phosphoribosyltransferase (NAMPT) is the rate limiting enzyme. In adipose tissue, the loss of NAMPT disrupts cold tolerance and systemic metabolic functions. NAMPT is an essential for survival gene and loss of NAMPT is lethal. The present study characterizes the metabolic changes of mice harboring a point mutation which results in a P158A mutation in the NAMPT protein. Adult (8-10 month) P158A mice exhibit a chronic NAD^+ deficit and reduced synaptic protein expression. However, adult or aged (19-20 month) P158A mice appear phenotypically similar to age-matched wild type (WT) mice, with only reduced grip strength observed at both ages. NAD^+ is important to many different pathways, we investigated whether P158A mice may experience any metabolic dysfunctions due to the low NAD^+ levels. Adult P158A mice do not display any metabolic or thermoregulatory dysfunction, however, aged P158A mice have impaired adaptive thermogenesis, manifesting by less capable to maintaining core body temperature both in response to diet restriction and acute cold exposure compared to age-matched WT mice. Moreover, aged P158A mice demonstrated increased glucose intolerance and insulin resistance. Given this, we tested whether P158A mutant mice were more susceptible to developing metabolic intolerances by placing them on a high-fat diet (HFD). After 12 weeks on HFD, adult P158A mice developed worse responses to glucose, insulin, and acute cold exposure stress tests. In summary, the current study suggests P158A mice exhibit global metabolic impairments and broaden our understanding of NAD^+ metabolism in health and diseases.

Disclosures: S. Lundt: None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.03/L25

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Effects of lactate utilization on sharp wave-ripple network activity in mouse hippocampal slices

Authors: *B. KHODAIE[1], L. SÖDER[1], A. LEWEN[1], A. ELGEZ[1], A. V. EGOROV[1], O. KANN[1,2];
[1]Inst. of Physiol. and Pathophysiology, Heidelberg University, Germany; [2]Interdisciplinary Center for Neurosciences (IZN), Heidelberg, Germany

Abstract: Lactate, once considered merely a metabolic waste byproduct, has emerged as a multifaceted player in neuronal function, serving both as an alternative energy source and a signaling molecule with diverse effects. Brain lactate levels can raise in various physiological and pathological contexts such as increased neuronal activity, physical exercise, ischemia, and neuroinflammation (e.g., multiple sclerosis and Alzheimer's disease). These changes can affect neuronal energy states, network excitability, and synaptic properties, as reflected in key hippocampal network patterns such as sharp wave-ripples (SPW-R) that are crucial for memory consolidation. Our study seeks to elucidate how lactate fuel affects network activity, synaptic transmission and intrinsic neuronal properties.To assess the impact of lactate on neuronal energy metabolism and network function, we used acute hippocampal slices of mice (4-6 weeks old), and varied the concentrations of glucose and lactate in the recording solution. Local field potential (LFP) recordings were performed in the CA3 and CA1 regions to investigate spontaneous SPW-Rs that associate with intermediate energy demand. Synaptic transmission was assessed by electrical stimulation of Schaffer collaterals or by monitoring baseline field activities in CA1. Simultaneously, sharp microelectrode recordings were used to evaluate the intrinsic properties of CA1 pyramidal cells.Our results revealed that 20 mM lactate was insufficient to substitute for 10 mM glucose as a sole energy source because it led to a reduction in both incidence and amplitude of SPW-Rs in CA3 and CA1, but it did not affect ripple frequency (>180 Hz). Interestingly, SPW-R incidence was already reduced by partial replacement of glucose with lactate (lactate/glucose ratio of >1:1). We also added the monocarboxylate transporter (MCT1/2) blocker AR-C155858 to 10 mM glucose, which led to a reduction in SPW-R incidence, without affecting SPW-R amplitude or ripple frequency. When AR-C155858 was added to 20 mM lactate, it strongly reduced SPW-R amplitude, frequency as well as incidence. Synaptic transmission at CA1 synapses showed a marked reduction when substituting 10 mM glucose with 20 mM lactate. However, intracellular recordings revealed only moderate changes in intrinsic firing properties of CA1 pyramidal cells under these conditions.In summary, lactate as a sole energy substrate is insufficient for maintaining SPW-R network activity and synaptic transmission in mouse hippocampal slices. However, MCT1/2 expression is important for metabolic flexibility of neuronal networks.

Disclosures: B. Khodaie: None. **L. Söder:** None. **A. Lewen:** None. **A. Elgez:** None. **A.V. Egorov:** None. **O. Kann:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.04/

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: DBT Govt of India Grant Support

Title: Inositol hexakisphosphate kinase-2 regulates energy dynamics and mitophagy via creatine kinase-B and PINK-1

Authors: *L. NAGPAL[1], M. D. KORNBERG[2], S. H. SNYDER[3];
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Abstract: Inositol hexakisphosphate kinases (IP6Ks) regulate various biological processes. To explore roles for IP6K2 in brain function, we elucidated its protein interactome in mouse brain revealing a robust association of IP6K2 with creatine kinase-B (CK-B), a key enzyme in energy homeostasis. Cerebella of IP6K2- deleted mice (IP6K2-knockout [KO]) produced less phosphocreatine and ATP and generated higher levels of reactive oxygen species and protein oxidative damage. In IP6K2-KO mice, mitochondrial dysfunction was associated with impaired expression of the cytochrome-c1 subunit of complex III of the electron transport chain. We reversed some of these effects by combined treatment with N-acetylcysteine and phosphocreatine. We also observed that IP6K2 is involved in attenuation of PINK-1-mediated mitochondrial autophagy (mitophagy) in the brain. Up-regulation of dynamin-related protein {Drp-1), as well as increased expression of mitochondrial biogenesis markers (PGCl-α and NRF-1) in the cerebella of IP6K2-deleted mice (IP6K2-knockout), point to the involvement of IP6K2 in the regulation of mitochondrial fission. Knockdown of IP6K2 also led to augmented glycolysis, potentially as a compensatory mechanism for decreased mitochondrial respiration. Overexpressing IP6K2 as well as IP6K2-kinase dead mutant in IP6K2-knockdown N2A cells reversed the expression of mitophagy markers, demonstrating that IP6K2-induced mitoprotection is catalytically/kinase independent. IP6K2 supplementation in K2-PINK1 double-knockdown N2A cells failed to reverse the expression of the mitophagic marker, LC3-II, indicating that the mitoprotective effect of IP6K2 is dependent on PINK-1. These findings establish a neuroprotective role for IP6K2.

Disclosures: L. Nagpal: None. **M.D. Kornberg:** None. **S.H. Snyder:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.05/L26

Topic: F.08. Food and Water Intake and Energy Balance

Support: ANID Grant 21210569
FONDECYT Grant 120-0474

Title: Youth exposure to sucrose plus a high-fat diet affects the μ-opioid receptor gene expression in the brain of adult rats in a sex-dependent manner.

Authors: *V. B. VELÁSQUEZ PINEDA[1,2], J. FIGUEROA JOFRÉ[1,3], G. E. TORRES, Sr.[4], R. SOTOMAYOR-ZÁRATE[1,2];
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Abstract: Obesity is a public health problem, produced by an energy imbalance, where the major factor involved is the consumption of high-fat, high-palatability food. Feeding is governed at the brain level by homeostatic and hedonic mechanisms; however, the impact of obesogenic food on the brain of infant and juvenile populations has been little studied. One of the receptors with great relevance in the modulation of feeding is the μ-opioid receptor (MOR), present in the lateral hypothalamus (LH), nucleus accumbens (NAc), and ventral tegmental area (VTA). Another interesting brain area to study is the lateral septum (LS), an eminently GABAergic area that regulates LH and VTA, which has not been studied under obese conditions. This work aimed to evaluate the effect of an obesogenic diet in juvenile rats of both sexes for six weeks on MOR gene expression in the LS, LH, NAc, and VTA. Sprague-Dawley rats were exposed from postnatal day (PND) 21 to PND 62 to chow plus water (control) or high-fat diet plus sucrose solution (HFD+S) ad libitum. Our data showed that HFD+S exposure decreased the MOR gene expression in LS of male rats relative to their controls. In contrast, the MOR gene expression was not affected by HFD+S in female rats. On the other hand, in NAc and LH, MOR expression was lower in females fed with HFD+S than in controls, while no significant differences were found in males. These data demonstrate that HFD+S exposure during adolescence modifies MOR gene expression in a sex-specific manner in several brain areas related to food intake. Further experiments are needed to determine whether these changes can affect MOR functionality concerning food intake in obesity.

Disclosures: V.B. Velásquez Pineda: None. **J. Figueroa Jofré:** None. **G.E. Torres:** None. **R. Sotomayor-Zárate:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.06/L27

Topic: F.08. Food and Water Intake and Energy Balance

Support: N° 21200338 “Beca de Doctorado Nacional” from ANID.
FONDECYT Grant N°120-0474
DIUV-CI Grant N°01/2006

Title: Exposure to hight fat diet plus sucrose solution alters gene expression of dopamine and CRF receptors in the lateral septum of sprague dawley rats

Authors: *R. OLIVARES-BARRAZA[1], J. ESCOBAR[2], V. B. VELÁSQUEZ[2], M. J. COVARRUBIAS[2], R. SOTOMAYOR-ZÁRATE[2];
[1]Univ. de Valparaíso, Valparaíso, Chile; [2]Inst. de Fisiología, Facultad de Ciencias, Univ. de Valparaíso, Valparaíso, Chile

Abstract: Obesity is a pandemic that has been associated with lifestyle changes, such as an increase in obesogenic food consumption and a decrease in physical activity. In addition, obesity induces dysregulations in brain areas that control feeding. In this context, the homeostatic and hedonic systems controlling food intake and are regulated by the lateral septum (LS). LS is a GABAergic relay nucleus whose efferents innervate the lateral hypothalamus (LH), nucleus accumbens (NAcc) and ventral tegmental area (VTA), among others. Also, LS neurons are regulated by several neurotransmitters and neuropeptides such as dopamine (DA) and corticotropin releasing factor (CRF), between others. The aim of this work was to study the effects of exposure to high fat diet plus sucrose solution (HFD+S) for 6 weeks in behavior (open field test) and LS gene expression of DA (D_1 and D_2) and CRF ($CRF_1$and CRF_2) receptors. Our results show that exposure to HFD+S increases locomotor activity in males and decreases locomotor activity in females, obtaining significant differences when comparing control males with females of both groups. In addition, the gene expression of D_1, D_2 and CRF_1 increase in LS, while the expression of D_1 and $GABA_B$ decrease in NAcc. Neurotransmission in both nuclei could be affected by changes in D_1 receptor expression, generating in LS an activation of GABAergic projections to LH and VTA. However, LS GABAergic interneurons could also be activated, which would reduce the activation of LS projection neurons. However, further studies are needed to test this hypothesis. Finally, the reduction in NAcc D_1 expression possibly affects the activation of the direct pathway, favoring food addiction.

Disclosures: R. Olivares-Barraza: None. **J. Escobar:** None. **V.B. Velásquez:** None. **M.J. Covarrubias:** None. **R. Sotomayor-Zárate:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.07/L28

Topic: F.08. Food and Water Intake and Energy Balance

Support: CONAHCYT A1-S-27322

Title: Analysis of the central blockade of IL-1β signaling on compulsive consumption of palatable food, neuronal activation and brain IL-1β expression in rats fed with a high-fat diet

Authors: M. CISNEROS CHIMAL[1], B. CONTRERAS[1], P. DE GORTARI[1], ***E. ALVAREZ**[2]; [1]Inst. Nacional de Psiquiatria, Mexico City, Mexico; [2]Mol. Neurophysiol., Inst. Nacional de Psiquiatria, Mexico City, Mexico

Abstract: Prolonged exposure to a high-fat diet (HFD) in animals can lead to the development of eating disorders, such as binge eating. Hedonic behaviors like the intake of palatable foods, are regulated in part by the mesolimbic dopaminergic system. Neuroinflammation, which main promoter is interleukin 1β (IL-1β), secondary to the consumption of a HFD, can damage this pathway generating a hypodopaminergic state. Inflammatory markers in the ventral tegmental area, hypothalamus and nucleus accumbens (NAc) have been associated with a compulsive food seeking behavior during binge eating episodes. To study the role of IL-1β receptor signaling in binge-like eating behavior in rats fed with a HFD, 52 adult male Wistar rats were fed with a control diet (**C**; 12% fat, n=26) or a HFD (**H**; 60% fat, n=26) for four weeks. To induce binge-like eating, animals were exposed to a highly palatable food (Oreo Double Stuf cookies) for 2 hours, three times per week. Prior to the last 2 binge episodes, the rats were injected into the left lateral ventricle with 2.5 µl of vehicle (**V**, n=25) or 0.5 µg of the IL-1β receptor antagonist (IL-1Ra, 0.2 µg/µL; **A**, n=27). Body weight and food intake were assessed during the binge episodes. Animals were euthanized and their brains collected and sectioned to obtain the NAc and hypothalamic areas. A double fluorescent immunohistochemistry was performed targeting the proteins c-Fos and IL-1β. Body weight was similar between groups throughout the experiment. Before surgery, there were no differences in caloric intake of chow or Oreo during the binge episode, between rats fed with either the control diet or HFD. After IL-1Ra injection, the HA rats were prevented from reducing the intake of palatable food as observed in HV; while HV rats decreased the intake of Oreo vs. CV. Interestingly, this effect was inverse for chow consumption, given that the intake of HA decreased vs. HV. Thus, it seemed that IL-1Ra administration allowed HFD-fed animals to have a similar eating pattern as controls during the binge episode. In contrast, IL-1Ra injection had no effect on food intake of controls, this may be explained by the absence of an underlying HFD-induced neuroinflammation (high expression of IL-1β). By the last binge episode, food intake was similar between groups, which revealed that IL-1Ra effect was short-lived. Neuronal activation was differently modulated in HFD-fed rats, in areas involved in the regulation of homeostatic and hedonic food intake behavior. These results suggest that the IL-1β inflammatory pathway plays a critical role in the binge for palatable food due to a HFD intake, which may impact the occurrence of eating disorders.

Disclosures: M. Cisneros Chimal: None. **B. Contreras:** None. **P. De Gortari:** None. **E. Alvarez:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.08/L29

Topic: F.08. Food and Water Intake and Energy Balance

Support: HKRGC-GRF 14112523
HKRGC-GRF 14113522
CUHK 7105306
CityU SGP Grant 9380157

Title: Exploring the neural correlates of thiamine homeostasis

Authors: *M. GAO[1], R. GOH[1], W. YUNG[2], Y. KE[1];
[1]The Chinese Univ. of Hong Kong, Shatin, Hong Kong; [2]City Univ. of Hong Kong, Kowloon, Hong Kong

Abstract: Thiamine deficiency, a type of hidden hunger due to inadequate dietary intake, can lead to abnormalities in the nerves, heart, and brain. Understanding the pathways of thiamine homeostasis can help elucidate how this deficiency is associated with neurological disorders such as Wernicke-Korsakoff syndrome. However, the neural mechanisms of thiamine perception remain unclear. Our project investigates the effects of thiamine deprivation on feeding behavior in mice and aims to uncover the underlying neural mechanisms. We established a thiamine deficiency model by providing mice with thiamine-deficient food for three weeks, which resulted in significant weight loss. To probe the ability to perceive thiamine, we conducted a food preference test where mice could freely choose to consume either thiamine-deficient or thiamine-containing food. The results demonstrated a strong preference for thiamine-containing food among the thiamine-deprived mice. Furthermore, we found that thiamine-deprived mice were more attracted to the odour of thiamine-containing food, suggesting that olfactory cues play a critical role in thiamine perception. We also discovered that neurons in the lateral parabrachial nucleus (LPB) showed increased c-Fos expression following prolonged thiamine deprivation. Interestingly, activation of these neurons was also observed in normally fed mice administered with thiamine solution, indicating that LPB activity is associated with the detection of physiologically abnormal thiamine levels. Overall, our findings suggest that mice can detect thiamine presence through olfaction and that fluctuations in thiamine levels are reflected in LPB neuron activity.

Disclosures: M. Gao: None. **R. Goh:** None. **W. Yung:** None. **Y. Ke:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.09/

Topic: F.08. Food and Water Intake and Energy Balance

Support: CONAHCYT

Title: Sex differences of C57BL/6 mice affect the binge-eating model.

Authors: *E. BARRERA-MIRANDA[1], S. ORTEGA-TINOCO[2], J. GARDUÑO[3], S. L. HERNANDEZ[4];
[1]Physiol., UNAM, Fac. of Med., Mexico City, Mexico; [2]Physiol., UNAM, Ciudad de México, Mexico; [3]Physiol., Univ. Nacional Autonoma de Mexico, Mexico, D.F., Mexico; [4]Physiol., Facultad de Med., Mexico, Mexico

Abstract: Standardized animal models represent a very important tool for understanding eating disorders nowadays, as they allow us to manipulate specific variables to study their effect on the development and progression of these disorders, following the DSM-V (Diagnostic and Statistical Manual of Mental Disorders). Binge eating disorder (BED) has the highest lifetime prevalence, ranging from 1.9% to 2.6% of all eating disorders in the US and worldwide, comparing it with anorexia nervosa (0.6%-0.8%) and bulimia nervosa (0.28%-1%) (Scradis & Arnow, 2023). BED is an intermittent and repeated overeating in brief periods, approximately 2-h (Corwin & Buda-Levin, 2004). In this case, we are using the binge eating model by Rebecca Corwin (Corwin, 2004), that help us to better understand certain behavior similarities in the response of Wistar rats to food. However, the model originally used only with male rats, can be implemented to both female and male C57BL/6 mice (30 days old), 16g to 20g. We used 30 subjects (n=15 male and n=15 female), who were placed in 3 groups as follows: Control (CTRL), with no access to shortening (n=5), with 24/7 *ad libitum* access to standard chow and water, continuous access (CA), with 24/7 *ad libitum* access to standard chow, water and M&M's, and intermittent access (IA) (n=5), with 24/7 *ad libitum* access to standard chow and water, but 2-hour limited access to M&M's every Monday, Wednesday, and Friday. The purpose of this study is not only to standardized the binge type model in male and female mice. Also clarify that although there are differences on behavior between sexes, as in body weight, water intake, standard food intake and palatable food intake, it is well handled in females.

Disclosures: E. Barrera-Miranda: None. **S. Ortega-Tinoco:** None. **J. Garduño:** None. **S.L. Hernandez:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.10/L30

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: FC2022-2024 PD

Title: Developmental, metabolic, and behavioral transgenerational impact in the offspring of dams exposed to a cafeteria diet during gestation and lactation

Authors: G. M. ROJAS MOSQUEDA, J. SANCHEZ MARTINEZ, ***D. BUSTAMANTE VALDEZ**, M. FUENTES-CANO, P. DURAN;
UNAM, Mexico City, Mexico

Abstract: Adequate nutrition from the first stages of development plays a fundamental role in the growth and health of mammals. The composition of the diet plays a crucial role in the development of the central nervous system, providing nutrients and energy resources necessary for its correct functioning, and integrating nutritional, hormonal, and neuronal signals to maintain an adequate energy balance in the body. Malnutrition (defined as an imbalance in the quantity and quality of diet), particularly intrauterine and early malnutrition, plays a crucial role in critical periods of development, resulting in physiological, cognitive, behavioral, and metabolic changes at various milestones. Malnutrition established using a "cafeteria diet" before and during pregnancy and lactation has been related to changes in metabolism and behavioral responses, although transgenerational effects have been poorly studied. This study aimed to evaluate the transgenerational effect of malnutrition (high-calorie/high-protein) during pregnancy and lactation on development, metabolism, and anxiety-like responses in the second offspring. Sprague-Dawley rats fed standard LAB rodent diet, separated into well-nourished (Wn), the first generation of malnourished, fed a cafeteria diet during pregnancy and lactation (MnF1), and the second generation of the MnF1 group, Malnourished F2 (MnF2), weight, height, early developmental markers, as well as glucose energy metabolism, and oxidative stress, were recorded and anxiety responses were assessed. The results showed a delay in growth, an increase in glucose levels and a decrease in anxious responses in the malnourished group, an effect that is conserved in the MnF1 and MnF2 generations. In conclusion, perinatal malnutrition due to a cafeteria diet produces maladaptive responses and programs energy and behavioral metabolism at various stages of development throughout life.

Disclosures: G.M. Rojas Mosqueda: None. **J. Sanchez Martinez:** None. **D. Bustamante Valdez:** None. **M. Fuentes-Cano:** None. **P. Duran:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.11/L31

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH MH136654
Brain and Behavior Research Foundation, Young Investigator Award

Title: Sex-dependent effects of high-fat diet content on food choice and neural activation

Authors: *T. A. MCCORKLE[1], A. K. SUTTON HICKEY[2];
[1]Psychology and Neurosci., [2]Dept. of Psychology and Neurosci., Temple Univ., Philadelphia, PA

Abstract: Energy-rich foods, such as those high in fat content, are increasingly prevalent in diets worldwide, likely due to their induction of a sustained devaluation of more nutritionally rich diets in favor of the more palatable high fat diets (HFDs). This heightened preference and corresponding intake for HFD are key risk factors for the development and maintenance of dysregulated feeding diseases including binge eating disorder and obesity. Moreover, this devaluation of standard diet (SD) has been demonstrated in rodents following exposure to animal-based HFD via the alteration of hypothalamic brain regions critical for regulating food intake via mesolimbic dopamine systems. While this suggests a connection between food choice behavior and brain systems governing homeostatic food intake, it is unclear how acute vs chronic exposure to multiple diet types might coordinate these effects. Additionally, although studies have illustrated the potential sex differences in HFD intake and associated weight gain this has not been interrogated in the context of food choice. Here, we conducted a 4-week behavioral paradigm wherein male and female mice were exposed to HFDs with varying fat compositions and ended with designated windows for HFD binge eating. Furthermore, we interrogated the neural correlates driving individual differences in HFD intake across biological sex by leveraging the TRAP-Fos-Cre mouse line crossed with a Cre-dependent TdTomato reporter line. Following the completion of behavioral tests, immunohistochemistry was performed to examine neural activity and sex differences associated with food choice. Our results demonstrated that male mice preferentially consumed a vegetable-based HFD upon initial exposure whereas female animals initially preferred an animal fat-based HFD, thus illustrating a biological sex difference in initial HFD preference. Throughout the study, the diet preferences in female mice remained consistent while male mice switched to the animal-based HFD. In both sexes, animals exposed to the HFDs significantly devalued SD. Experiments to elucidate the neural correlates of these findings from the post-hoc brain tissue, especially in hypothalamic regions, are currently ongoing. Collectively, our findings offer invaluable insight into biological sex-dependent food preferences and neural activity patterns that may underlie certain addictive food behaviors exhibited in individuals experiencing dysregulated feeding diseases.

Disclosures: T.A. McCorkle: None. **A.K. Sutton Hickey:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.12/L32

Topic: F.08. Food and Water Intake and Energy Balance

Support: Director's Innovation Fund, TJL

Title: High-fat diet induces region- and cell-specific brain lipid, metabolite, and peptide changes measured by high-resolution mass spectrometry imaging in mice

Authors: B. N. GURDON, A. DUNN, T. ZHAO, T. STODOLA, B. HOFFMANN, ***K. O'CONNELL**;
The Jackson Lab., Bar Harbor, ME

Abstract: Obesity affects over 40% of adults in the United States and is a risk factor for a host of other diseases, such as diabetes, heart disease, and stroke. Obesity is associated with dysfunction in appetite circuits in the brain that regulate food intake and energy expenditure. Our previous work has shown that even short-term consumption of an obesogenic high-fat diet (HFD) leads to long-lasting changes in hypothalamic neuronal excitability and food intake behavior. Long-term consumption of a HFD has also been associated with changes to neuroinflammation and cognition, circadian disruption, and altered risk for cognitive decline and dementia with aging; however, these effects are often variable and the underlying mechanisms responsible for behavioral and disease outcomes following consumption of a HFD are not fully understood. Using mass spectrometry imaging (MSI), we have investigated brain-wide lipid, metabolite, and peptide abundance to facilitate a mechanistic understanding of the factors influencing brain health and function in mice fed a normal control diet (NCD), a high-fat/high-sugar diet (HFHSD), or high-fat diet (HFD). We have observed intriguing alterations in the relative abundance of lipid species throughout the brains of mice fed a HFD and HFHSD diet. These changes vary across cell types and brain regions, suggesting that there is significant heterogeneity in the response of various cells and regions to dietary factors. These studies reveal regions, cell types, and subcellular structures that may be particularly vulnerable to diet-induced changes, as well as molecular factors that may be responsible for the array of behavioral and neurological outcomes in individuals fed a HFD or HFHSD.

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Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.13/Web Only

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH DK131892
NIH DK119130
NIH DK131870
NIH GM103430-SURF
Provost's Faculty Fellowship, Providence College

Title: Additive, non-intersectional action of hypothalamic hunger circuits overcomes cost for acquisition of food

Authors: *R. J. POST[1,2], M. KINDEL[2], N. GOLDSTEIN[2], N. K. SMITH[2], J. BETLEY[2]; [1]Psychology & Neurosci., Providence Col., Providence, RI; [2]Biol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Adaptive behavior requires changing behavioral strategies based on the relative cost of each action. Such behavioral plasticity is essential for survival, yet how the brain influences these calculations is not fully understood. To model how food consumption changes in a dynamic world, we used multiple assays that impose different and quantifiable environmental or energetic costs to obtaining food and then assessed consumption. We found that hunger drives mice to overcome significant costs to obtain food, and that the behavioral effects of hunger are completely recapitulated by activity in arcuate nucleus (ARC) Agouti-related peptide (AgRP)-expressing neurons (n = 18 male and female mice across experiments). Optogenetically activating individual AgRP neuron projections does not lead to the same behavioral shifts observed in hunger (n = 31 male and female mice across experiments). However, simultaneously activating multiple AgRP subpopulations demonstrates that AgRP projections are additive in their ability to increase motivation to obtain food as cost increases (n = 21 male and female mice across experiments). Using calcium imaging, we find that hunger does not inhibit signals of environmental cost in AgRP projection target regions (n = 19 male and female mice across experiments). Instead, this information is relayed to cortical ensembles and the emergence of behavior correlates with the relative strength of each individual need. Taken together, these findings demonstrate that the previously observed redundancy in hunger networks is necessary to increase 'hunger pressure' that ensures food intake when the cost of obtaining food is high. Our data suggest the unanticipated conclusion that adaptive food intake occurs not through the selective filtering of competing signals of need, but rather by a simultaneous weighting of the two needs that shifts cortical activity to feeding-specific ensembles in situations of starvation.

Disclosures: R.J. Post: None. **M. Kindel:** None. **N. Goldstein:** None. **N.K. Smith:** None. **J. Betley:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.14/L33

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH MH 136654
Brain and Behavior Research Foundation, Young Investigator Award
The Mid-Atlantic Neuroscience Diversity Scholars (MiNDS) program

Title: Determining the behavioral adaptations and neural correlates of food insecurity in mice

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Abstract: Eating disorders (ED) are deadly psychiatric illnesses characterized by severe and persistent disturbances in feeding behaviors. Food insecurity, defined as the economic and social condition of limited or uncertain access to adequate food, has been identified as a key risk factor for ED pathogenesis. Yet, the causative impact of food insecurity on future behaviors, and the underlying neurobiology driving these effects are not fully understood. Our goal is to measure how rodent behavior is impacted both during and after unexpected food availability by establishing a food insecurity paradigm in mice. We hypothesized that the mice that underwent food insecurity would lose the most body weight due to decreased food intake, and that subsequent food motivation would be increased. Mice were assigned to either a control group with ad libitum access to food (Ad Lib) or an experimental group with access to food at random timeouts (Random), with daily measurements of body weight, and continuous monitoring of food intake and physical activity using the Feeding Experimental Device 3 (FED3) and the Rodent Activity Detector (RAD), respectively. Following baseline, 4 experimental days began in which mice in the Random cohort experienced random timeouts in between food pellets whereas the Ad Lib cohort remained in the "Free Feeding" condition. All mice were then returned to baseline conditions, after which mice underwent operant tasks (Fixed-Ratio 1 and closed-economy progressive ratio) . Our results indicate that mice in the Random condition decreased food intake both during the initial stages of the dark cycle as well as after baseline conditions were returned, with reduced motivation for food pellets in comparison to the Ad Lib group across both the light and dark cycles. We are continuing to investigate these alterations in motivation, along with the neural correlates coordinating these effects, by including tests investigating how prior exposure to variable food access might drive anhedonia. These results suggest that exposure to variable food access might drive a chronic depressive-like phenotype in mice, and thus has implications for how food insecurity might impact future behavior and the neurobiology coordinating feeding behavior.

Disclosures: K. Mendez: None. **T.A. McCorkle:** None. **A.K. Sutton Hickey:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.15/Web Only

Topic: F.08. Food and Water Intake and Energy Balance

Support: MEXT/JSPS KAKENHI Grant 22K09900
JST SPRING Grant JPMJSP2119

Title: Possible involvement of the nervous system for conditioned taste aversion in the mechanism of feeding disorder.

Authors: *Z. WEI, H. HUANG, T. YOSHIZAWA, T. INUI, M. FUNAHASHI;
Hokkaido Univ., Sapporo, Hokkaido, Japan

Abstract: We investigated the rejection behavior to sweetened diet containing saccharin in rats acquired conditioned taste aversion (CTA) to saccharin solution. Usually, after rats that have acquired CTA to saccharin solution, they avoid ingestion of saccharin solution despite being thirsty due to water deprivation for 21 hours and 40 minutes. In other words, it is thought that the drinking behavior induced by thirst was suppressed by the memory of aversion to taste. In the present study, we hypothesized that rats avoid consuming sweet diet despite being hunger sensation due to food deprivation for 22 hours and 40 minutes. We measured changes in the amount of diet and fluid intake, and body weight before and after CTA acquisition in male Sprague-Dawley rats (7 weeks of age). Saccharin solution (0.1%) was used as a conditioned stimulus. Emetine dihydrochloride (5.54 mg/kg, 1% BW, i.p.) and cisplatin dihydrochloride (3mg/kg, 1% BW, i.p.) were used as unconditioned stimulus that can induce nausea. In the control group of rats, saline (1% BW, i.p.) was used instead of emetine or cisplatin. In some rats conditioned with cisplatin, we examined the effects of ondansetron (5-HT3 receptor antagonist, 0.1 mg/kg, 0.1% BW, i.p.) and maropitant (neurokinin-1 receptor antagonist, 2 mg/kg, 0.1% BW, i.p.) at 30 minutes before conditioning or teat days. The sweet diet was prepared by mixing normal solid diet with an equal amount of 0.2% saccharin solution. Normal diet was also processed in the same way to match the texture. After a recovery day following CTA acquisition, the amount of sweet diet intake was measured for five days (test 1-5). The emetine-treated group showed a significant decrease in sweet diet intake in the test 1-4 as compared to the conditioning day ($F(5,30) = 4.644$, $P < 0.05$, Dunnett's test). The cisplatin-treated group showed a significant decrease in sweet diet intake in the test 1 and 2 ($F(5,48) = 2.976$, $P < 0.05$, Dunnett's test). We also found that the amount of normal diet intake was not significantly reduced in test 1-5. Pre-administration of ondansetron abolished the decrease in sweet diet intake in the cisplatin group. In the control group, sweet diet consumption was rather increased in the test 3-5 compared to conditioning days. These results indicate that eating behavior was suppressed in rats with hunger sensation if they had acquired CTA to sweetness of saccharin. It was also suggested that this feeding suppression occurs by the nervous system involving the 5-HT3 receptors. We concluded that the central mechanism of CTA is possibly involved in the eating disorders such as anorexia nervosa.

Disclosures: Z. Wei: None. **H. huang:** None. **T. Yoshizawa:** None. **T. Inui:** None. **M. Funahashi:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.16/L34

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NSF-CAREER 2141330

Title: Adult brain stem cells and the relationship to hypothalamic neural plasticity and metabolic health

Authors: *K. TOWNSEND, T. TAO;
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Abstract: Adult neural plasticity, which includes the generation of adult-born cells in the brain, allows the nervous system to respond to physiological changes, injuries, and environmental stimulation. Adult neurogenesis is now known to occur outside classic brain niches, including in the hypothalamus, where adult stem cells differentiate to neuroblasts and appetite-regulatory neurons that are responsive to nutritional status. Our lab investigates two putative stem cell populations in the adult hypothalamus: 1) telomerase reverse transcriptase (TERT)-expressing adult quiescent stem cells, and 2) hypothalamic tanycytes - specialized glia that line the third ventricle and interface with the blood vasculature, cerebrospinal fluid, and hypothalamic appetite neurons. We previously demonstrated that TERT marks multipotent adult stem cells that are largely quiescent at the basal state. Given the presence of TERT-positive stem cells in hypothalamus, we utilized caloric restriction (CR) as a stimulus for neural plasticity. scRNAseq data from TERT-lineage traced cells following 30% CR revealed a plasticity enhancing gene expression program across numerous cell types. Interestingly, the hypothalamic niche was particularly responsive to CR. Tanycytes are radial glial-like cells implicated in glucose-sensing and stem cell-like behavior, and we found tanycytes in the same niche as TERT+ cells but tanycytes did not express TERT or lineage-trace from TERT+ cells. To determine alternate signaling pathways regulating tanycyte plasticity, we explored bone morphogenetic protein receptor 1A (BMPR1A), which is highly and tightly co-expressed along the tanycyte barrier. BMP7, a BMPR1A ligand, is implicated in body weight control, appetite, and energy expenditure, and BMPs are well-known to impact neurogenesis and neural plasticity. We explored whether BMPR1A is important for tanycyte stem cell behavior and metabolic control by generating tanycyte-specific BMPR1A knockout mouse models. We found that ablation of BMPR1A in adult hypothalamic tanycytes affected food intake. Finally, we are investigating therapeutic effects of TERT+ cells or tanycytes as cell therapies in a penetrating brain injury model. Taken together, TERT+ cells and tanycytes are involved in adult hypothalamic plasticity, and BMPR1A-mediated signaling in tanycytes likely links neural plasticity to metabolic control.

Disclosures: K. Townsend: None. **T. Tao:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.17/L35

Topic: F.08. Food and Water Intake and Energy Balance

Support: CIHR Grant PJT-153009
NSERC Grant RGPIN-2017-05184

Title: High dietary salt amplifies constitutive cell proliferation and adult neurogenesis in sensory circumventricular organs

Authors: *P.-M. CHEVILLARD[1], S. ZHOU[2], O. MAKASHOVA[1], G. CHEN[1], C. LAPORTE[1], A.-I. HICKS[1], M. PRAGER-KHOUTORSKY[1];
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Abstract: Adult neurogenesis proceeds through adulthood in the subventricular zone and hippocampal subgranular zone. Median eminence (ME) and adjacent medio-basal hypothalamus, two hypothalamic regions controlling energy balance, are additional areas containing neural stem cells (NSCs) that give rise to new neurons and glia in the adult brain. The ME is one of the circumventricular organs (CVOs), which are specialized brain areas featuring an incomplete blood-brain barrier, thereby mediating crosstalk between the central nervous system and the peripheral circulation. Additional CVOs located in the hypothalamus are the Organum Vasculosum of Laminae Terminalis (OVLT) and the Subfornical Organs (SFO). The OVLT and SFO contain neurons which are activated in response to increased blood osmolality and sodium, thereby playing a central role in the regulation of hydromineral balance, thirst, and autonomic and cardiovascular functions. Whether the OVLT and SFO harbor adult NSCs remains unclear. Here, we demonstrate the existence of constitutive cell proliferation in the OVLT and SFO of adult rats. We show that NG2 glia, tanycytes, and pericytes proliferate in these CVOs. The OVLT and SFO also contain populations of newborn neurons, which can differentiate and express mature neuronal markers. Importantly, we show that the proliferation of glia cells and the generation of newborn neurons are amplified in rats fed high salt diet. These findings show that adult glial proliferation and neurogenesis persist in the OVLT and SFO and the rate of these processes is modified by diet-induced changes in the hydromineral balance, potentially contributing to the regulation of body fluid homeostasis.

Disclosures: P. Chevillard: None. **S. Zhou:** None. **O. Makashova:** None. **G. Chen:** None. **C. Laporte:** None. **A. Hicks:** None. **M. Prager-Khoutorsky:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.18/L36

Topic: F.08. Food and Water Intake and Energy Balance

Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)-Brasil - Finance Code 001
National Council for Scientific and Technological Development - CNPq – Brazil Process: 201014/2022-0

Title: Dehydration-induced hypothalamic non-coding RNA expression pattern in neurons of the supraoptic nucleus

Authors: E. PEREIRA JUNIOR[1], G. LEYDEN[2], M. P. GREENWOOD[2], S. BÁREZ-LÓPEZ[3], C. A. ANDRADE[1], *J. MENANI[1], D. MURPHY[2];
[1]UNESP, Araraquara, Brazil; [2]Univ. of Bristol, Bristol, United Kingdom; [3]Univ. of Madrid, Madrid, Spain

Abstract: The neural processes mediated by hypothalamic nuclei are central to the maintenance of physiological homeostasis. The hypothalamic Giot1 RNA has emerged as a potential key regulator of the adaptive and behavioural responses underlying osmoregulatory balance in the rat model of osmotic stress. However, the spatio-temporal dynamics of Giot1 RNA expression are still unknown, which will provide greater information in understanding its functions. Here, we characterize the hypothalamic expression of the Giot1 RNA to identify subcellular regions of WKY rat vasopressinergic (AVP) and oxytocinergic (OXT) magnocellular neurons (MCNs) that express Giot1 in hydrated and water deprived rats (n=10). Giot1 RNA expression in the supraoptic nucleus (SON) was quantified using RNAScope in situ hybridization in AVP and OXT MCNs. Water deprivation for 72 h led to an increase in the expression of Giot1 RNA in the cytoplasm and nucleus of AVP and OXT neurons, when compared to hydrated rats. However, this expression was higher in AVP neurons when compared to OXT (AVP - cytoplasm: 0.240 ± 0.043 vs. OXT cytoplasm: 0.0472 ± 0.0147; AVP nucleus: 0.643 ± 0.107 vs. OXT nucleus: 0.067 ± 0.027). Furthermore, it was observed that after dehydration there was a greater expression of Giot1 RNA in the nucleus of AVP neurons when compared to the expression in the cytoplasm (Nucleus: 0.643 ± 0.107 vs. Cytoplasm: 0.240 ± 0.043). In summary, the results show that Giot1 is expressed in AVP and OXT neurons in the SON and that after osmotic stimulation by water deprivation there is a significant increase in the expression of Giot1 RNA, with this increase being greater in the nucleus of AVP neurons.

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Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.19/Web Only

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Effect of arsenic exposure on the vasopressin pathway in adult rodent brain, osmolar homeostasis and neurotoxicity

Authors: *L. RAMOS[1], M. LEON-OLEA[2,3];
[1]Inst. Nacional De Psiquiatría Ramón De La Fuen, PEDREGAL DE CARRASCO, Mexico;

[2]Martha Leon Olea, Mexico D.F., Mexico; [3]Neuromorfología Funcional, Instituto Nacional de Psiquiatría Ramón de la Fuente, Mexico, Mexico

Abstract: Arsenic (As) is a ubiquitous semimetal and neurotoxic contaminant with global epidemiological importance. As can cause multi-organ cancer, neurotoxicity and cardiovascular alterations, specifically by increasing blood pressure. The metabolism of As leads to a cellular pro-oxidant state, the main mechanism of As damage. Additionally, it has been reported that oxidative stress alters the metabolism of nitric oxide (NO), a second cellular messenger, gaseous neurotransmitter that participates in memory and cardiovascular control. NO is a regulator of vasopressin (AVP, antidiuresis) that control blood pressure; maintain osmolarity and vasoconstriction, especially during osmolar challenges. *In vivo* studies have suggested that AVP participates in working and spatial memory, as well as in neurodegenerative processes. Therefore, in this work we assess the neurotoxic effect of As on AVP in adult female and male rats and mice. Animals were exposed to 20 ppm of As in the drinking water. No differences in body weight between control and As exposed. After 30 days of exposure, animals were subjected to osmolar challenge; subgroups of each experimental condition were subjected to normosmotic (*free* access to tap water) and hyperosmotic challenge (*ad libitum* access to 2% saline solution, for 5 days). Serum osmolarity were quantified at baseline and against osmolar challenge. Preliminary results suggest an increase in the baseline osmolarity (5.9%, 18 mOsm/kg) in As-exposed male rats and an increase tendency in females (6.3%, 19 mOsm/kg), with no changes in the mice model. These findings could be especially useful in describing the molecular mechanism underlying the neurotoxicity and increase in blood pressure associated with the ingestion of water contaminated with As.

Disclosures: L. Ramos: None. **M. Leon-Olea:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.20/L37

Topic: F.01. Neuroethology

Support: NSF (CRCNS 1822550; 2203119)
Vannevar Bush Faculty Award (ONR N000142012828)

Title: A neuronal ensemble regulating water homeostasis in Hydra vulgaris

Authors: *W. YAMAMOTO, R. YUSTE;
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Abstract: *Hydra* is a cnidarian with a simple, distributed nervous system comprising just a few hundred neurons. As one of the few cnidarians to successfully colonize freshwater environments, its cells constantly accumulate water due to osmosis. Failure to remove excess water leads to osmotic shock and cellular rupture. To prevent this, *Hydra* removes excess water, first into its

gut-like gastric cavity, and then to the exterior, through its mouth. To do so efficiently, *Hydra* needs robust mechanisms to sense osmotic pressure and water accumulation, and to coordinate neuronal activity and muscle contractions to excrete the excess water. The neural and molecular mechanisms behind this water excretion process are still unknown. This homeostatic adaptation offers a compelling model for investigating brain-body interactions and the evolution of interoception circuits at the cellular and molecular levels. Given the anatomical structure of the animal, where the endoderm lines the gastric cavity, we investigated the role of an endodermal ensemble of neurons known as rhythmic potential 2 (RP2). Using *Hydra* expressing a fluorescent calcium indicator, we found that RP2 neuronal activity increased during body contractions and water excretion. Two-photon ablation of RP2 neurons decreased spontaneous contractions and body length. Moreover, preliminary experiments using two-photon stimulation of RP2 neurons showed body widening and water excretion, consistent with their causal role in water homeostasis. Ongoing research aims to uncover the sensory receptors and trace the evolutionary pathways of these brain-body interacting systems through biochemical and bioinformatic analysis.

Disclosures: W. Yamamoto: None. **R. Yuste:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.21/M1

Topic: F.01. Neuroethology

Support: NIH Grant U19NS104653
SNSF Grant P2SKP3_187684

Title: Cold acclimation provides a robust overwintering strategy in Hydra vulgaris

Authors: *C. DUPRE[1], F. ENGERT[2];
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Abstract: Cold acclimation is a biological process that allows animals to survive at low temperatures. The freshwater invertebrate Hydra is subject to broad changes in environmental temperature and does not have the required motility in order to move to warmer environments during the winter. For this reason, Hydra had to develop robust mechanisms to achieve cold acclimation at the onset of winter. How Hydra detects the onset of winter and activates its acclimation mechanism is unknown.
Here, we used thermocyclers to induce cold acclimation in Hydra and study its properties. We found that Hydra cultured at room temperature (RT) do not survive an abrupt transition from 22°C to 4°C. However, they can be treated to become cold acclimated and survive at 4°C by exposure to intermediate temperatures such as 12°C if the treatment duration exceeds more than a week. Once cold acclimated, Hydra is considerably more robust to thermal changes. It survives

repeated abrupt transitions from 4°C to 22°C and 22°C to 4°C. However, acclimation is reversible and if a cold acclimated Hydra stays at room temperature for more than a week it will gradually lose its cold acclimation. We developed a mathematical model representing the dynamics of this process and used it to predict survival according to temperature data recorded in one of their natural habitats. The results of these simulations provide an explanation for how Hydra survives winter under natural conditions. Accordingly, daily fluctuations are too short to cause injury, and seasonal fluctuations, which are long enough to be lethal, allow acclimation to incrementally build up and protect the animal. Cold acclimation in Hydra is therefore an example of a strategy that has adapted during evolution to match the animal's needs for survival.

Disclosures: C. Dupre: None. **F. Engert:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.22/M2

Topic: F.06. Autonomic Regulation

Support: The Mathers Foundation # MF-2204-02555 (Machado)
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Brain & Behavior Research Foundation Young Investigator Grant (Kucukdereli)
National Institute of Health, R01DK096010-09A1 (Lowell)

Title: A hypothalamic circuit for fasting-induced torpor

Authors: A. DOUGLASS[1], H. KUCUKDERELI[2], D. MELVILLE[3], L. ANGENENDT DA COSTA[5], N. LYNCH[4], A. BANKS[4], C. B. SAPER[6], B. LOWELL[4], *N. MACHADO[4];
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Abstract: Many animals utilize a survival strategy of hypothermia, inactivity, and a dramatic decrease in their energy metabolism when faced with a shortfall in energy supplies. Mice, for example, show daily torpor that may last several hours to bridge the lack of energy availability in a cold environment. However, the neural basis for this adaptive modulation of thermoregulatory and metabolic responses is still enigmatic. We hypothesize that the energy state of animals is conveyed to thermoregulatory neurons located in the preoptic region of the hypothalamus by inputs from the arcuate nucleus (ARC), a region known to be indispensable for driving metabolic

and behavioral adaptations to the fasted state.We report here that inputs from the ARC drive the activity of median preoptic neurons (MnPO) that produce energy conservation in times of food scarcity. We found that ARC- Agouti-Related Peptide (AgRP) neurons, but not ARC-Pro-Opiomelanocortin (POMC) neurons, have an increase in intracellular calcium during fasting-induced torpor bouts, and their release of Neuropeptide Y (NPY) and GABA enables hypothermic responses during starvation. Activating the ARC^{AgRP}→MnPO pathway (n=5) induces a decrease in body temperature in both *ad libitum* (AL) or food deprived (FD) conditions (max change: -2.5 ± 0.4 °C SEM AL vs -3.1 ± 0.8 °C SEM FD), reduces energy expenditure (max change: -0.14 ± 0.04 Kcal/h SEM AL vs -0.1 ± 0.02 Kcal/h SEM FD) and suppresses brown adipose tissue thermogenesis (max change: -2.5 ± 0.3 °C SEM AL). Critically, the inhibition of the ARC^{AgRP}→MnPO brain circuit entirely prevents fasting-induced torpor. Our results suggest that MnPO neurons integrate information about the animal's nutritional state through inputs from ARC^{AgRP} neurons to produce a hypometabolic state and reduce thermoregulatory costs in response to energy depletion.

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Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.23/M3

Topic: F.06. Autonomic Regulation

Support: JSPS Grant-in-Aid for Scientific Research (C)

Title: Intermittent skin cooling affects melatonin secretion from the pineal gland in anesthetized rats

Authors: *N. WATANABE, M. MORIYA, H. HOTTA;
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Abstract: The pineal gland is an endocrine organ that synthesizes and secretes melatonin, regulated by the cervical sympathetic nerve. Somatosensory stimulation, including thermal stimulation, reportedly modulates autonomic nerve activity and affects hormone secretions. We investigated whether thermal stimulation to the skin influences melatonin secretion from the pineal gland in anesthetized rats. Male Fischer rats were anesthetized with urethane. A microdialysis probe was inserted into the pineal gland, and phosphate-buffered saline was perfused at a rate of 1 μL/min. Perfusate was collected every 20 minutes, and the melatonin concentration was quantified by ELISA. A Peltier thermode was attached to the trunk skin to apply thermal stimulation, changing the temperature repeatedly between 30°C and 15°C, for 20 minutes. Without stimulation, melatonin concentration was stable over the sampling period.

Melatonin concentration did not change during thermal stimulation; however, it tended to decrease following the termination of stimulation (at 0-20 minutes post-stimulation). Melatonin concentration gradually returned towards the pre-stimulation level. The present results suggest that mild thermal stimulation applied to the rat's trunk skin may decrease melatonin secretion from the pineal gland. Neural mechanisms, including the contribution of the cervical sympathetic nerve, will be examined.

Disclosures: N. Watanabe: None. **M. Moriya:** None. **H. Hotta:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.24/M4

Topic: F.06. Autonomic Regulation

Support: Canadian Institutes of Health Research (FDN-148413)

Title: Mechanistic investigation into the role of neurotensin in hypothermia and hypotension

Authors: *F. LUSSIER[1], F. BELAIR[2], J. COTE[3], M.-A. DANSEREAU[1], J.-M. LONGPRE[4], D. BLONDIN[1], P. SARRET[5];
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Abstract: Neurotensin (NT) is an endogenous tridecapeptide that produces a prolonged, dose-dependent decrease in core body temperature through interaction with two G-protein coupled receptors, namely NTS1 and NTS2. Harnessing its hypothermic properties may represent a promising approach to generate therapeutic and protective hypothermia in the setting of cardiac arrest or ischemic stroke. However, the pharmacological management of hypothermia by NT and its analogs is hampered by their ability to induce hypotensive effects. A better understanding of the underlying mechanisms leading to hypothermia and hypotension following NT receptor activation could therefore help distinguish between desired and unwanted physiological effects. Here, we hypothesized that biased agonism represents an opportunity for developing drugs with a greater benefit/risk balance and could provide key insights into the signaling pathways associated with hypothermia and hypotension. To this end, a series of NT analogs selected from the literature were studied for their ability to modulate various signaling pathways using BRET-based biosensors, as well as for their potential to induce hypothermic and/or hypotensive responses. We found that these NT analogs exhibited distinct intracellular signaling profiles at NTS1, produced significant changes in body temperature (-1 to -3°C) and induced marked drop in mean arterial pressure (0 to -80 mmHg). However, to date, the signaling signature of these NT derivatives was not directly linked to their physiological efficacy in lowering body temperature

and blood pressure. To gain further insight into the central and peripheral role of NTS1 and NTS2 in body temperature regulation, we also investigated the effects of the knockdown of NTS1 and NTS2 in the median preoptic nucleus (MnPO), a key structure involved in thermoregulation and blood pressure control. We also evaluated their functional role in controlling the central response when subjected to selective or non-selective NTS1/NTS2 analogs and different ambient temperatures. Finally, we intend to explore the relationship between the neurotensinergic and histaminergic, the latter being known to be involved in both hypotensive and hypothermic responses. Overall, these results will help decipher the mechanisms leading to neurotensin-induced hypothermia to ultimately provide a better rationale for future drug development efforts.

Disclosures: F. Lussier: None. **F. Belair:** None. **J. Cote:** None. **M. Dansereau:** None. **J. Longpre:** None. **D. Blondin:** None. **P. Sarret:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.25/M5

Topic: F.06. Autonomic Regulation

Support: NS111378
NS117148
NS116383

Title: Tbi disrupts core temperature dynamics and metabolic thermogenesis

Authors: *B. DA CRUZ WEBER FULCO[1], P. VANDER[2], Z. YING[3], S. CORREA[4], F. GOMEZ-PINILLA[5];
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Abstract: Traumatic brain injury (TBI) is a significant global health concern, leading to death and long-term disability. TBI patients exhibit loss of temperature control that can affect all functions in brain and body, reduce functional recovery, and quality of life. Maintaining controlled normothermia is crucial in TBI management to reduce mortality and prevent neurological complications. We have implemented an animal model to study how TBI influences metabolic thermogenesis response to a cold challenge. We used implantable temperature transmitters to assess real-time temperature in animals exposed to moderate lateral fluid percussion (FPI). We found that FPI induced acute hypothermia, slowly returning to baseline after 12 hours. TBI animals also reduced amplitude of circadian rhythmicity until post-injury day 3. At 7 days post-TBI, a subset of animals was exposed to a 4 ºC cold chamber, to assess their thermoregulatory capabilities. In contrast to the Sham group, characterized by a gradual decline

in temperature throughout the challenge, the TBI animals exhibited a pronounced drop in temperature until around the 3rd hour. Thermal imaging of brown adipose tissue (BAT) site showed a constant temperature drop until the end of the challenge in TBI group, indicating altered thermoregulation in response to cold exposure. Transcriptomic analysis was used to determine genes associated with control of temperature regulation in the liver, BAT, and subcutaneous white adipose tissue (subWAT). We found in the TBI group a decrement in mRNA levels of thermoregulatory and lipolytic genes in BAT (*Ucp1, Dio2, Elovl3, Lipe and Mgll*), subWAT (*Ucp1, Dio2* and *Elovl3)* and liver (*Apoa4, Cpt1a, Cpt1b, Fgf21, PPARGC1A* and *THRβ*). Furthermore, we observed a decrease in mitochondrial proteins levels (Ucp1 and OxPhos) in TBI group suggesting impaired BAT non-shivering thermogenesis (NTS). Although BAT serves as the primary site for NST, compromised BAT function prompts skeletal muscles to serve as an alternative site. Moreover, we found increased mRNA levels of genes involved in skeletal muscle NTS (*SERCA1, SERCA2, SLN* and *Ucp3*) in TBI group. In summary, TBI disrupts body temperature regulation affecting circadian rhythmicity and responses to cold exposure, as evidenced by compromised BAT function, as well as impaired hepatic and subWAT cold adaptation responses. The increase of thermogenesis-related genes in skeletal muscles post-TBI suggest a compensatory response to impaired thermoregulation, emphasizing the systemic impact of TBI on physiological body states.

Disclosures: B. Da Cruz Weber Fulco: None. **P. Vander:** None. **Z. Ying:** None. **S. Correa:** None. **F. Gomez-Pinilla:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.26/M6

Topic: F.06. Autonomic Regulation

Support: Grant-in-Aid for Transformative Research Areas from JSPS (23H04941)
JST FOREST Program, Grant Number JPMJFR2066

Title: Slowing sepsis in mice with a hibernation-like state induced by excitation of QRFP-positive neurons in the hypothalamus.

Authors: *G. A. SUNAGAWA, A. WATAKI, K. ISHIKAWA, M. MATSUMOTO, S. FUJINO, H. ONO;
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Abstract: Hibernation is a state of regulated hypometabolism where animals reduce their basal metabolic rate and lower body temperatures to survive winter food shortages. Theoretically, inducing a similar decrease in metabolic demand in critically ill patients could mitigate oxygen shortages in tissues and slow disease progression. However, the challenge of inducing hibernation instantly in animals has hindered testing this hypothesis.

In 2020, our team discovered that activating QRFP-containing neurons (Q neurons) in the mouse hypothalamus induces a hibernation-like state called QIH (Q neurons-induced hypometabolism) (Takahashi TM et al., *Nature*, 2020). QIH can be triggered on-demand through chemogenetic or optogenetic stimulation of Q neurons, and we have demonstrated its ability to protect organs from ischemic damage (Kyo S et al., *JTCVS Open*, 2022).
This study demonstrates that QIH effectively slows sepsis progression, even with a four-hour delay post-sepsis induction. Furthermore, QIH enhances the effectiveness of standard sepsis treatments, presenting a novel approach to managing sepsis and inflammation.
However, previous studies have shown that hibernation weakens the immune system (Bouma HR, *J Leukoc Biol*, 2010). How do our findings fit into this context? One possibility is that Q neurons that induce a hibernation-like state can activate the organism's final defense mechanism or the agonal state.
To further understand this possibility, we quantified the neurons activated in the hypothalamus during sepsis. While septic animals typically become hypometabolic and hypothermic, which should deactivate Q neurons, we found that septic animals had a higher number of cFos-positive neurons in the QIH-activated area than control animals. This counterintuitive finding suggests that the lowered metabolism and body temperature observed during sepsis result from Q neuron activation but not the sickness.Our results not only highlight the therapeutic potential of hibernation-like states in sepsis management but also contribute to a deeper understanding of the interplay between the Q neurons-induced hibernation-like states and sickness behavior.

Disclosures: G.A. Sunagawa: None. **A. Wataki:** None. **K. Ishikawa:** None. **M. Matsumoto:** None. **S. Fujino:** None. **H. Ono:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.27/M7

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: USDA/CRIS (3092-51000-062-04(B)S

Title: Dissect the role of ERα^{POA} neuron subpopulations in thermoregulation

Authors: *Y. DENG[1], M. YU[1], *Q. LIU[1], N. ZHANG[1,2], Y. XU[1], *C. WANG[1];
[1]Dept. of Pediatrics, Baylor Col. of Med., Houston, TX; [2]Dept. of Endocrinol., Tongji Med. Col., Hubei, China

Abstract: Thermoregulation is vital for maintaining homeostasis among various physiological functions, including circadian rhythm, stress responses, and energy balance. It is established that the preoptic area of the hypothalamus (POA) is the central hub of thermoregulation. The POA temperature closely follows ambient and core temperature changes. In addition, the POA integrates peripheral temperature signals and local temperature sensing to control body

temperature and other thermoregulation-related behaviors such as temperature preference and valence. Recent studies revealed both warm- and cold-sensing neurons in the POA, suggesting the heterogeneity of POA thermoregulatory neurons. Estrogen receptor alpha (ERα) is abundantly expressed in the POA, and it is reported that a group of $ER\alpha^{POA}$ neurons could be activated by increased ambient temperature. However, it is not clear whether the thermoregulatory $ER\alpha^{POA}$ neurons are homogenous, and the relative contribution of $ER\alpha^{POA}$ neuron subpopulations towards thermoregulation is unknown. Interestingly, our findings demonstrated that thermoregulatory $ER\alpha^{POA}$ neurons could be further divided into warm- and cold-activated subpopulations, and we hypothesize that these two subpopulations play distinct roles in thermoregulation. In the current study, we combined 'Targeted Recombination in Active Populations (TRAP)' and intersectional Cre_{on}-Flp_{on} expression system to specifically dissect the roles of warm- and cold- activated $ER\alpha^{POA}$ neuron subpopulations in body temperature regulation, temperature preference, and valence. We found that environmental cold-activated $ER\alpha^{POA}$ neurons can also be activated by temperature decrease of the bath solution surrounding these neurons. This result for the first time provides proof-of-concept that $ER\alpha^{POA}$ neurons are regulated by temperature changes from both the external environment and the internal brain. Importantly, we found that while activation of general $ER\alpha^{POA}$ neurons significantly reduced body temperature in mice, specific activation of cold-activated $ER\alpha^{POA}$ neuron subpopulation did not induce any alternation in body temperature. Instead, once activated, these neurons produced strong negative valence, as measured by conditioned place-preference test. These findings demonstrate that distinct $ER\alpha^{POA}$ neuron subpopulations contribute to the different aspects of thermoregulation.

Disclosures: Y. Deng: None. **M. Yu:** None. **Q. Liu:** None. **N. Zhang:** None. **Y. Xu:** None. **C. Wang:** None.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.28/M8

Topic: F.01. Neuroethology

Support: NIH Grant R01 GM130842-01

Title: Absolute temperature sensors in the brain drive behavioral thermoregulation in drosophila larva.

Authors: *S. LAZOPULO[1], A. D. SAMUEL[1], P. A. GARRITY[2];
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Abstract: The ability to control body temperature provides survival advantages and homeotherms like birds and mammals have developed physiological mechanisms of thermoregulation. Yet both homeotherms and poikilotherms implement strategies to regulate

their body temperature behaviorally. One of the fundamental thermoregulatory behaviors is thermotaxis - a voluntary movement towards preferred temperature. Behavioral thermoregulation is a motivated, decision-based, homeostatically controlled process, like drinking and eating. It is realized by integrating two types of thermosensory information: internal temperature, used for the feedback when the body temperature deviates from the set point; and external temperature, used for the feedforward to anticipate potential changes in body temperature. Previous works have identified the molecular and neuronal feedforward sensors in Drosophila larva head that detect temperature changes. Here we identified a subset of neurons in the larval brain that provide feedback about internal absolute temperature. We designed a combination of techniques to study larval behavior and neuronal activity in response to temperature variation at different absolute values. Using targeted knockdowns and isoform-specific rescues we found that TRPA1(A) is required for adjusting the response to temperature variation. Using calcium imaging, we measured temperature response of the TRPA1-expressing neurons of a live-mounted larva. We identified a subset of absolute thermosensory neurons (ATns) in the latero-posterior part of the brain showing responses to a varying temperature in a range of temperatures between 18^{o}C and 30^{o}C. We registered phasic responses in the synaptic terminals of the ATns and tonic responses in cell bodies. Knockdown of *trpA1* in the ATns results in failure for both behavioral and neuronal responses to temperatures above 24^{o}C, but not below. This suggests potential expression of multiple temperature receptors that together span the full range of responses. Next, we identified ATns in the whole-brain neuronal connectivity map (connectome) and established their location in the thermosensory circuit. ATns project to Lateral Horn, a well-established control center for innate behaviors, and are two steps downstream of the peripheral thermosensors. Connectome data provides possible site of integration of different temperature inputs and allows us to further model the behavior on a quantitative level. In conclusion, our results provide new insights into the thermosensory behavior of larvae and a potential for uncovering new integrative processes and neuronal circuits that orchestrate animal thermotaxis.

Disclosures: S. Lazopulo: A. Employment/Salary (full or part-time):; Harvard University. **A.D. Samuel:** A. Employment/Salary (full or part-time):; Harvard University. **P.A. Garrity:** A. Employment/Salary (full or part-time):; Brandeis University.

Poster

PSTR355: Thermoregulation, Ingestion, Neurometabolism, and Neurogenesis

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR355.29/M9

Topic: F.01. Neuroethology

Support: NIH/NINDS Grant 1F31NS129270

Title: Evolution of temperature preference behavior in Drosophila

Authors: *M. CAPEK[1], O. M. ARENAS SABOGAL[2], M. H. ALPERT[1], I. MENDEZ GONZALEZ[1], H. GIL[1], A. ACOSTA[1], J. M. SIMÕES[1], Y. SU[1], A. PARA[1], M. GALLIO[1];

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Abstract: How preference for a given temperature range evolves during the colonization of new environments is not known. Here, we show that at least two distinct neurobiological mechanisms drive the evolution of temperature preference in flies of the genus *Drosophila*. Fly species from mild climates (such as *D. melanogaster* and *D. persimilis*) avoid heat, and we show that this can be fully explained by differences in the activation threshold of peripheral hot receptor neurons. In contrast, desert-dwelling *D. mojavensis* are instead attracted to heat. We demonstrate that this is due to a valence switch, from aversive to attractive, in how the brain processes input from the peripheral receptors. Although insects are ubiquitous, few species inhabit thermal extremes. Our findings illustrate how adaptation to desert life in *Drosophila* involved a remarkable rewiring of the thermosensory system.

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Poster

PSTR356: Neural Circuits II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.01/M10

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

Support: NSTC-112-2628-B-A49-013

Title: Basal forebrain encoding of reward prediction error is temporally coupled with and caused by activities in midbrain dopamine neurons

Authors: *Y.-J. JHONG[1], M.-C. CHIANG[2], M. KUO[2], S.-C. LIN[1,3,4];
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Abstract: The discrepancy between received and expected rewards, commonly known as reward prediction error (RPE), is the central driving force of reinforcement learning. In the brain, the neural encoding of RPE has been traditionally associated with the activity of midbrain dopaminergic (DA) neurons. However, several recent studies found similar RPE characteristics in the activity of a distinct subset of noncholinergic basal forebrain (BF) neurons, referred to as BF bursting neurons. These observations raise the question of whether midbrain DA neurons and BF bursting neurons convey two independent RPE signals, or whether their activities are coupled with each other. Here we show that the activity of BF bursting neurons is not only temporally

coupled with but also driven by the activity of midbrain DA neurons with a robust 10-msec temporal delay. Using simultaneous recording of both midbrain and BF neurons in freely-moving rats performing associative learning tasks, we found strong correlations of neuronal response amplitudes and timing between putative DA neurons and BF bursting neurons in single trials. Activities of DA neurons were consistently about 10 msec earlier than those of BF bursting neurons, regardless of whether the behavioral task was well-trained or under new learning. To further test whether the observed correlation reflected a causal relationship, we optogenetically stimulated DA neurons in DAT-cre mice and found robust excitation of many BF neurons at latencies around 10 msec. Most DA-activated BF neurons showed phasic excitation toward reward-predicting stimuli and corresponded to BF bursting neurons. Together, these results reveal a novel causal coupling between midbrain DA neurons and BF bursting neurons, and support the idea that the brain uses two major neuromodulatory systems to jointly encode RPE.

Disclosures: Y. Jhong: None. **M. Chiang:** None. **M. Kuo:** None. **S. Lin:** None.

Poster

PSTR356: Neural Circuits II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.02/M11

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

Support: NSTC-112-2628-B-A49-013

Title: Rapid and biphasic modulation of reward-seeking behaviors by basal forebrain glutamatergic neurons that project to the lateral habenula

Authors: *K.-Y. TING[1], S.-C. LIN[1,2];
[1]Inst. of Neuroscience, Natl. Yang Ming Chiao Tung Univ., Beitou Dist., Taipei City, Taiwan;
[2]Brain Res. Center, Natl. Yang Ming Chiao Tung Univ., Beitou Dist., Taipei City, Taiwan

Abstract: The lateral habenula (LHb) is an important brain region that negatively modulates reward-seeking behaviors. A prominent input of the LHb comes from vGluT2-expressing glutamatergic neurons in the basal forebrain (BF). While recent studies have shown that strong excitations of LHb or its glutamatergic inputs from the BF suppress reward-seeking behaviors, how BF vGluT2 neurons modulate reward-seeking behaviors on a fine temporal scale remains unclear. Here we show that transient optogenetic activations of LHb-projecting BF vGluT2 neurons rapidly and biphasically modulate reward-seeking behaviors. We trained head-fixed vGluT2-cre mice to lick for water reward after auditory cues, and probed the influence of BF vGluT2 neurons on licking behaviors by optogenetically activating BF vGluT2 neurons with a brief 10ms light pulse at different time points of this behavior. We found that the brief activation of BF vGluT2 neurons reliably modulated licking responses, resulting in a rapid and biphasic modulation that consisted of an initial suppression followed by a brief facilitation of licking

behaviors. Moreover, this biphasic modulation can be observed when BF vGluT2 neurons were optogenetically activated at either soma or axon terminals in the LHb. To further understand the neural circuit mechanisms that mediate this behavioral effect, we simultaneously recorded BF neuronal activities and found that optogenetic activation of BF vGluT2 neurons, either at the soma or their axon terminals in the LHb, reliably modulated the activity of a distinct group of BF putative GABAergic neurons in a rapid and biphasic manner, consisting of an initial inhibition followed by a brief excitation. Since the activity in this distinct group of BF putative GABAergic neurons has been linked to promoting reward-seeking behaviors in recent studies, their biphasic modulation by BF vGluT2 neurons provides a likely mechanism that may mediate the biphasic effects of BF vGluT2 excitation on reward-seeking behaviors. Together, our results reveal how BF vGluT2 neurons rapidly and biphasically modulate reward-seeking behaviors, and suggest that such modulations likely involve a biphasic modulation of BF neuronal activities via vGluT2 projections to the LHb.

Disclosures: K. Ting: None. **S. Lin:** None.

Poster

PSTR356: Neural Circuits II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.03/M12

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

Support: NSTC-112-2628-B-A49-013

Title: Optogenetic augmentation of basal forebrain responses improves auditory detection and reward expectation

Authors: *H.-C. LIU[1], S.-C. LIN[1,2];
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Abstract: Detecting environmental cues that signal potential rewards is essential for survival. Recent studies have shown that reward-predicting stimuli phasically activate a distinct subset of neurons in the basal forebrain (BF), referred to as BF bursting neurons, and such BF phasic responses predict successful detection and faster decision speeds. Moreover, the BF phasic response toward sensory stimuli quantitatively conveys a reward expectation signal, which is negatively correlated with the response of BF bursting neurons toward reward delivery. Despite their strong correlation with behavioral performance, whether BF phasic responses play a causal role to promote reward-seeking behaviors remains unclear. Here, using cell-type specific optogenetic activation in head-fixed mice, we selectively augmented BF bursting responses to reward-predicting stimuli and show that the behavioral performance in an auditory detection task is substantially enhanced. We first identified Npas1 and Npr3 as markers for a novel subset of

GABAergic BF neurons and found that a brief 10-msec optogenetic activation of BF Npas1 or Npr3 neurons elicited phasic excitation that selectively engaged all BF bursting neurons. In an auditory detection task in which head-fixed mice licked for water reward after detecting sound stimuli presented at various intensities levels, the brief optogenetic activation of BF Npas1 or Npr3 neurons delivered at the onset of sound stimuli significantly increased the phasic response amplitudes of all BF bursting neurons toward sound stimuli. This manipulation substantially improved detection probabilities toward sound stimuli at various intensities, as well as enhancing decision speeds. In addition, there was a significant reduction in the response of BF bursting neurons toward reward delivery, even though the optogenetic stimulation was delivered only at sound onset. Together, these results support a causal role of BF phasic responses in promoting reward-seeking behaviors and suggest that optogenetic augmentation of BF bursting response improved behavioral performance through enhancing animals' reward expectation towards the detected stimuli.

Disclosures: H. Liu: None. **S. Lin:** None.

Poster

PSTR356: Neural Circuits II

Location: MCP Hall A

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Program #/Poster #: PSTR356.04/M13

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

Support: ERC Starting Grant 715043
NAP3.0 (NAP2022-I-1/2022)
NKFIH K147097

Title: Correlations in neuromodulatory codes during different learning processes

Authors: *B. KIRÁLY, V. PILLÁR, F. BENYÓ, A. BENKE, B. HANGYA;
Inst. of Exptl. Med., Budapest, Hungary

Abstract: Neuromodulatory systems, more specifically dopamine, noradrenaline, serotonin, and acetylcholine, can dynamically change brain states and rapidly alter information processing of large number of neurons. Therefore, they can play a crucial role in cognitive functions, including learning and memory, and are accordingly severely implicated in neurodegenerative diseases such as Alzheimer's or Parkinson's diseases. Interestingly, neuromodulatory systems often regulate seemingly overlapping cognitive processes and show similar modes of action. To reveal possible synergistic or antagonistic relations and to better understand the exact role of these systems, in a comprehensive series of experiments, we simultaneously monitored pairs of neuromodulatory systems using either the combination of fluorescent neuromodulator sensors and fiber photometry or optogenetic tagging and electrophysiology techniques in mice performing a series of behavioral tasks focusing on different aspects and mechanisms of learning such as psychometric operant learning and implicit statistical learning. Therefore, we first

designed and trained mice in three novel learning tasks, an auditory operant conditioning task (n = 30), a gambling bandit task (n = 28) and a sequential serial reaction time task (n = 23). In the examined subcortical target areas (the ventral striatum and the basolateral amygdala), we observed robust event related release of dopamine and acetylcholine, linked to behavioral feedback and outcome predictions in all tasks, which closely resembled the spiking activity of the deep brain neuronal source (the ventral tegmental area and the diagonal band of Broca) of the corresponding neuromodulators. On the other hand, neuromodulator release in the prefrontal cortex was more characterized by an oscillatory alteration of neuromodulator release (demonstrated by autocorrelation analyses) but also in a task-dependent manner, entrained by behaviorally salient events. Cross-correlation analyses revealed a correlated but not fully synchronous activity between acetylcholine and dopamine in all examined brain areas, which scaled with reward prediction error across all learning mechanisms, while a negative correlation was observed between acetylcholine and serotonin release.In conclusion, our results suggest that multiple modes of learning rely on a precisely coordinated release of various neuromodulators, which act on a heterogeneous manner across different brain areas, as we surprisingly found characteristic differences between cortical and subcortical neuromodulatory signals.

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Poster

PSTR356: Neural Circuits II

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Program #/Poster #: PSTR356.05/M14

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

Support: ERC Grant 715043

Title: Investigating the role of neuromodulators in mice during associative learning with a 50% reward schedule

Authors: *I. SZABO, R. KISPAL, B. KIRÁLY, A. VELENCEI, B. HANGYA;
Inst. of Exptl. Med., Budapest, Hungary

Abstract: The concept of reward prediction error (RPE), defined by the difference between an actual and expected reward, serves as a cornerstone in reinforcement learning theory for updating value representations and driving behavioral adaptations. It is well known that the dopaminergic system represents RPE, but our understanding of the correlation between other neuromodulatory systems and RPE remains limited. Our study aimed to explore the involvement of neurotransmitters dopamine (DA), acetylcholine (ACh), norepinephrine (NE), and serotonin (5-HT) in associative learning, alongside their correlation with RPE. Using an auditory Pavlovian conditioning task with a 50% reward schedule, we investigated clean representations of positive (rewarded trials) and negative RPE (omission trials) in mice, while concurrently measuring

neurotransmitter release via fiber photometry. DA release was measured in both the prefrontal cortex (PFC) and ventral striatum (VS), and ACh/NE/5-HT release in both the PFC and basolateral amygdala (BLA). Behavioral adaptation based on previous trial outcomes was measured through mice licking activity in anticipation of reward. Consistent with expectations, anticipatory lick rate (ALR) decreased during stimulus presentation following omission trials but increased after rewarded trials. This pattern was mirrored by DA release and observed not only in the VS but also in the PFC. Additionally, significant positive correlations were observed between DA release and ALR in both brain regions. Similarly, ACh release followed the RPE changes in the BLA and the PFC. Conversely, NE and 5-HT release in the PFC decreased post-reward and increased post-omission trials, while it tracked RPE updates in the BLA. Our findings showed that the dopaminergic system transmits RPE signals to both striatal and frontal cortical targets. The cholinergic system signals unsigned prediction error, and we showed that it also demonstrates a trial-by-trial update, akin to DA. The noradrenergic and serotonergic systems in the BLA demonstrate a correlation with RPE, suggesting their involvement in associative learning processes. However, in the PFC, these systems exhibit divergent activity, possibly due to variations in innervation patterns from distinct subareas of the primary neuromodulatory regions.

Disclosures: I. Szabo: None. **R. Kispal:** None. **B. Király:** None. **A. Velencei:** None. **B. Hangya:** None.

Poster

PSTR356: Neural Circuits II

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Program #/Poster #: PSTR356.06/M15

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

Support: NIH 5RO1NS078294-10

Title: Functional roles of glutamatergic neurons in the basal forebrain towards encoding and assigning valence

Authors: *P.-S. CHIN[1], B. R. ARENKIEL[2];
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Abstract: The behavior of most organisms is shaped by their internal representation of the external world. Mammals primarily acquire information about the environment through sensory systems, and this information is meticulously processed by a network of interconnected brain regions. The basal forebrain, traditionally recognized as an arousal center, has recently been identified as capable of sensing environmental cues and playing a key role in top-down regulation of sensory stimuli. It is composed of diverse neuronal populations, including cholinergic, GABAergic, and glutamatergic neurons, all of which form reciprocal connections within the basal forebrain. Previous research indicates that glutamatergic neurons in the basal

forebrain play crucial roles in guiding feeding, avoidance, and other behaviors. However, how this population encodes sensory stimuli to guide behaviors remains unknown. Towards this, we performed *in vivo* calcium imaging in awake mice to record population responses of basal forebrain glutamatergic neurons ($vGlut2^{BF}$) while presenting different odor stimuli. We implemented a linear decoder trained on general population responses to elucidate different odor identities. The initial decoding showed poor performance, suggesting that odor identities are not innately embedded within this population. However, after paring odors with aversive stimuli, the average responses to the conditioned odors increased, and the decoding performance significantly improved, suggesting that the representation of value in the basal forebrain emerges with association. Given that associative learning altered the $vGlut2^{BF}$ neuron dynamics, we asked if this population is necessary for olfactory learning. Towards this, we conducted an odor association task while selectively inhibiting $vGlut2^{BF}$ neurons using genetically targeted expression of DREADD receptors. With inhibition, significantly more trials were required for mice to learn a single odor pair, suggesting this population is necessary for olfactory learning. Also, we tested whether pairing stimulation of $vGlut2^{BF}$ neurons with distinct odors for three days would influence odor preference. Indeed, we found that mice exhibited selective aversion to odors paired with the stimulation, suggesting these neurons are sufficient to generate a negative association with odor stimuli to alter preference behaviors. Overall, we found that conditioning changes populational response of $vGlut2^{BF}$ neurons to better encode odor identity, and that excitatory projection neurons within basal forebrain are sufficient to guide odor preference through generating new associations and/or assigning valence.

Disclosures: P. Chin: None. **B.R. Arenkiel:** None.

Poster

PSTR356: Neural Circuits II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.07/M16

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

Title: A disinhibitory basal forebrain to cortex projection supports sustained attention

Authors: *S.-J. LI[1,2], B. HANGYA[3], U. GUPTA[1], A. KEPECS[1];
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Abstract: Sustained attention is essential for survival and critical for navigating life. However, sustaining attention over time requires effort and is vulnerable to periodic lapses that manifest as fluctuations in performance. Yet the specific neural circuits underlying sustained attention are still unclear. The basal forebrain (BF) is largely known for its cholinergic population implicated in cognitive disorders. But recent evidence challenges the proposed dominant role of its signature cholinergic neurons in tracking attention fluctuation. By combining quantitative behavior, neural

circuits, and computational approaches, we demonstrate that the circuitry and function of another major output population in the basal forebrain — parvalbumin-expressing (BF-PV) inhibitory neurons exhibit key properties supporting sustained attention. First, on the circuit level, we determined that BF-PV neurons project topographically to the neocortex and modulate cortical gain through disinhibition. To test their behavioral functions, we monitored both the spikes of individual BF-PV neurons using optogenetically-assisted electrophysiology and the corresponding cortical terminal activity in multiple cortical target regions (auditory and motor cortex) using fiber photometry. In a mouse sustained attention task, we found that the activity of BF-PV neurons predicted performance metrics such as reaction time and accuracy. Furthermore, optogenetic stimulation of BF-PV neurons enhanced task performance, indicating a causal role in modulating attention. BF-PV neurons also responded to motivationally significant events in cued-outcome tasks: predictive cues, rewards, punishments, and surprises. To interpret the complex response properties of BF-PV neurons, we developed a computational model that encapsulates the concept that diverse BF-PV neuron responses reflect motivational salience, which guides attention allocation and provides a comprehensive framework for understanding attentional resource constraints. In summary, our study reveals a disinhibitory basal forebrain-to-cortex projection that regulates cortical gain based on a motivational salience computation, thereby promoting sustained attention.

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Poster

PSTR356: Neural Circuits II

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.08/M17

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

Support: PhD Fellowship from the Argentine National Research Council (CONICET)
National Agency for the Promotion of Research, Technological Development and Innovation Grant (BID PICT 2020-03449)

Title: Reward modulation of primary visual cortex and basal forebrain activity

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Abstract: The primary visual cortex (V1) is the first station for cortical processing of visual information and its neural activity is related to basic features of visual stimuli. Plasticity of visual responses in adults is thought to be limited to ensure reliable and reproducible sensory

processing. However, plastic changes induced by experience enhance visual responses and may improve visual processing in the adult. Also, when rodents experience an association between a visual stimulus and a contingent future reward, a proportion of V1 neurons develop reward timing activity. This suggests that V1 neural activity may also be related to the processing of the behavioral significance that stimulus acquires in the context of a task. Cholinergic projections from the basal forebrain (BF) have been shown to be necessary and sufficient to induce V1 reward timing activity. Furthermore, it is known that BF cholinergic neurons play an important role in associative learning and respond to reward acquisition. However, little is known about how this activity evolves with training and if BF neurons show reward timing activity. To unveil this, we implanted C57BL/6 adult male mice in V1 and BF and recorded electrophysiological activity in mice learning a visually cued rewarded task. We trained head-fixed mice (n=4) to initiate a lick sequence after a visual cue (LED) presentation to obtain a water reward in 70% of the trials. To determine how behavior and neural responses evolve during training, we compared early (E) and late (L) sessions. Animals successfully learned the task, showing a decrease in the latency to initiate the lick sequence (E:0.97 vs L:0.61 sec, $p<0.05$ paired *t* test), and an increase in correct trial completion (E:62 vs L:92%, $p<0.05$ paired *t* test) and reward rate (E:2.7 vs L:4.1 rewards/min, $p<0.05$ paired *t* test). As previously reported, we identified 32% of V1 neurons that showed reward timing activity late in training. Additionally, we found that BF neurons show prominent responses to different events in the task: LED, reward acquisition (REW) and reward omission (O). Surprisingly, we also observed sustained BF responses up to the time of expected reward (reward timing, RT). The proportion of neurons responding to LED and REW did not change across training (LED, E:33/116 vs L:45/223; REW, E:44/116 vs L:98/223 neurons). While, responses to O and RT increased with training (O, E:18/116 vs L: 75/223 neurons, χ^2 test $p<0.05$; RT, E:10/116 vs L:65/223 neurons, χ^2 test $p<0.05$). These findings suggest that V1 plasticity interpreted in a reinforcement-learning framework may be induced by BF neural activity, further emphasizing the role of BF neurons in associative learning.

Disclosures: M.F. Santos: None. **C.L. Zold:** None.

Poster

PSTR356: Neural Circuits II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.09/M18

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

Support: NIH IRP

Title: Neuron clusters in sensory and emotional processing regions co-project to orbitofrontal cortex and caudate, suggesting a possible role in value normalization

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Inst. of Mental Hlth. (NIMH), North Bethesda, CA; [4]Lab. of Neuropsychology, NIMH, Bethesda, MD; [5]NIMH, Bethesda, MD

Abstract: Using retrograde Lentivirus (FuG-E) injections, we mapped neuron clusters throughout the nonhuman primate brain in which individual neurons co-project to orbito-frontal cortex (OFC) and rostromedial caudate (rmCD). These two regions are of interest because the of their role in stimulus value and reward processing. Connections from various brain regions to each of these two regions are well documented. However, patterns of co-projections via forking axons are less well known. We find that some of the clusters with the largest percentage of co-projecting neurons are found in the basal and basomedial amygdala, where up to 25% of the OFC projecting neurons also project to rmCD, and up to 15% of rmCD projecting neurons also project to OFC. Other regions with a large percentage of co-projecting neurons are found in the medio-dorsal thalamus, the parahippocampal cortex, insular cortex, and various regions of IT cortex. Maybe somewhat unexpectedly, in the same regions, we also consistently find individual co-projecting neurons in the contralateral hemisphere, with an even larger percentage of neurons in the same regions projecting to OFC also projecting to rmCD. This distribution seems consistent with a normalization signal required for hypotheses that stimulus-reward responses are adaptively adjusted via a divisive normalization.

Disclosures: W. Lerchner: None. **A. Luz-Ricca:** None. **C. Chang:** None. **M.A. Eldridge:** None. **B.J. Richmond:** None.

Poster

PSTR356: Neural Circuits II

Location: MCP Hall A

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Program #/Poster #: PSTR356.10/M19

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

Support: NIH IRP: ZIAM# H002619

Title: Neurons co-projecting to IT cortex and striatum play a potential role in divisive normalization

Authors: *C. CHANG, W. LERCHNER, B. LI, M. A. ELDRIDGE, B. J. RICHMOND; NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD

Abstract: Throughout the brain, neural signals encoding reward value play a critical role in assigning context-dependent saliency to sensory stimuli during behavioral decision-making. This process requires some mechanism for normalization, with divisive normalization being a prime candidate. In a previous study, we discovered clusters of neurons in visual and emotional processing areas, like the basal amygdala, that co-project to the orbitofrontal cortex (OFC) and the rostromedial caudate (rmCD) of striatum; these regions process relative value and reward prediction respectively. Such shared feed-forward projections suggest the aforementioned areas are communicating normalization information, but divisive normalization would also require a

reciprocal signal to be sent back to sensory regions. Therefore, our current study investigated feed-back projections to higher-order visual processing regions, specifically areas TE and TEO of the inferotemporal (IT) cortex. Retrograde lentiviruses were injected into these two areas, as well as into posterior striatal (pST) regions known to receive IT cortex input, namely the tail of caudate (CDt) and posterior putamen (Pu). Following histological analysis, one of the strongest clusters of neurons co-projecting to pST and IT cortex was again identified in the basal amygdala. Further characterization revealed that 64% of all neurons projecting to pST from the basal amygdala also project to IT cortex, including some that project to all three regions of interest. Overall, these triple-projecting neurons constitute 5% of all observed striatum-projecting neurons, 4% of all observed TE-projecting neurons, and 7% of all observed TEO-projecting neurons. A particularly robust ratio of triple-projecting neurons was found in the parvocellular division of the basal amygdala, where 41% of striatum-projecting neurons project to both TE and TEO. In general, TEO-striatum co-projections appear more abundant anteriorly and in the magnocellular division of the basal nucleus, whereas TE-striatum co-projections become more prevalent posteriorly and within the intermediate division of the basal nucleus. Such anatomical differences in the distribution of co-projecting neurons suggest that distinct regions within the basal nucleus have varied roles in processing visual-reward information. In addition to the basal amygdala, large clusters of neurons co-projecting to IT and pST were identified in the prefrontal cortex (PFC) and claustrum—regions involved in attentional control, salience detection, and other cognitive processes relevant to decision-making and goal-oriented actions.

Disclosures: C. Chang: None. **W. Lerchner:** None. **B. Li:** None. **M.A. Eldridge:** None. **B.J. Richmond:** None.

Poster

PSTR356: Neural Circuits II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.11/M20

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

Title: Differential value coding of learning from gains and losses in multiple prefrontal areas

Authors: *C. TASWELL[1], S. WANG[2], B. B. AVERBECK[2];
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Abstract: Adaptive behavior requires learning to gain rewards and avoid losses. Most work on learning has focused on learning to gain rewards. Therefore, we have developed a paradigm that allows us to examine whether the same or different neural systems underlie learning from gains vs. losses. We have previously shown that Ventral Striatum (VS) plays a specific role in learning to select between rewarded outcomes (Taswell, Costa et al. 2018). In a follow-up study we found that the learning deficits VS monkeys displayed in (Taswell, Janssen et al. 2023) was due to motivation, and not learning ability. Additionally, in this same study, we showed that monkeys with lesions to the amygdala performed as well as controls. These results suggest that the neural

circuitry that underlies learning values associated with gains vs. losses differs. In the present study, we recorded single and multiunit activity using 3 microelectrode arrays (96 channels per array) implanted in the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), and ventrolateral prefrontal cortex (VLPFC). In addition to these arrays, we also simultaneously recorded single and multiunit activity using 2 microelectrode arrays (64 channels per array) implanted in the anterior cingulate cortex (ACC). Activity was simultaneously recorded in these areas while monkeys completed a stochastic token reinforcement learning experiment (Taswell, Costa et al. 2018). In this experiment, we conditioned tokens as reinforcers in a task where animals could both gain and lose tokens. We introduced four novel images in each block which had associated outcomes of +2, +1,-1,-2 tokens. Seventy-five percent of the time the outcome was the value of the cue, and 25% of the time the outcome was 0. Monkeys had to learn over trials, in each block, the outcomes associated with each cue, and choose the best cue in each trial.

Disclosures: C. Taswell: None. **S. Wang:** None. **B.B. Averbeck:** None.

Poster

PSTR356: Neural Circuits II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.12/M22

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

Support: NIH Grant 1R01MH130755
Emory URC

Title: Determining the role of local interneurons in shaping the reward responses in the medial prefrontal cortex

Authors: *H. BALASUBRAMANIAN[1], J. ISAAC[2], M. MURUGAN[3];
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Abstract: Identifying and processing the value of a rewarding scenario is crucial to determining appropriate behavioral reactions. Previous studies investigating the neural basis of reward processing in the brain have widely cited the medial prefrontal cortex (mPFC) as a critical node in mediating, both social, and non-social reward related behaviors. Recent findings reveal that in mice, both social and nonsocial reward representations in the mPFC are encoded by distinct neural ensembles. However, the contribution of the various cell types to these reward ensembles remains unknown. First, it is unclear if individual excitatory and inhibitory interneurons in the mPFC exhibit shared or distinct representations of social and non-social reward. Second, the role of the local inhibitory interneurons in modulating the reward representations and behavior remains unexplored. Interneurons, unlike excitatory neurons, can exhibit mixed selectivity to stimuli, indicating a shared representation of reward. We tested this possibility by parcellating the role of the parvalbumin (PV) interneurons in the mPFC that have causal effects on social

behaviors and nonsocial reward seeking. Through cellular resolution calcium imaging, we monitored the activity of over 150 PV interneurons across 5 male mice while they chose between social and non-social rewards in a self-paced (social-sucrose) operant assay. In contrast to expectations of mixed selectivity, we found that significantly non-overlapping populations of PV interneurons responded to social and non-social reward than expected by chance. By using linear dimensionality reduction techniques, and comparing the mahalanobis distance between neural responses to each reward, we verified separable neural representations even at a population-level. We also identified that PV neuronal activity can significantly decode both the choice the being made, and the reward being consumed. These results suggest that unlike sensory cortices, mPFC PV interneurons in the context of reward processing display selectivity in responses and could possess specific connectivity within social and nonsocial reward ensembles. Additionally, by performing cellular resolution calcium imaging in the excitatory population in the mPFC and by verifying our hypothesis of the internal circuitry between these neurons in a computational network model, we aim to deduce a microcircuit-level representation of the reward in the mPFC.

Disclosures: H. Balasubramanian: None. **J. Isaac:** None. **M. Murugan:** None.

Poster

PSTR356: Neural Circuits II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.13/M23

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

Support: R01MH126022

Title: Uncovering the spatiotemporal dynamics of dopamine in mouse dorsal cortex

Authors: *T. SZAPARY, C. I. JAHN, J. PARK, T. BUSCHMAN;
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Abstract: Dopamine (DA) has been implicated in learning, motivation, and motor control. Most studies have focused on the mesostriatal and mesolimbic pathways but we still lack a clear view of the dynamics of DA across the mesocortical pathway. Here, we leveraged the recent development of DA sensors (GRABDA) in combination with widefield imaging of the dorsal cortex to measure the spatiotemporal dynamics of DA release. Mice passively observed common (80%) and uncommon visual stimuli (20%) and received rewards at unpredictable times. We found dissociable lick and reward-related increases in DA release that heterogeneously propagated in the retrosplenial-secondary motor cortex and somatosensory cortex respectively. Visual stimuli were associated with a widespread negative ramp of DA release in the dorsal cortex, which was modulated by the stimulus probability only in the visual cortex. Preliminary data from an operant conditioning task found the DA response to instrumental licks gradually increased as the animals learned the task. This suggests cortical DA is recruited during learning and goal-directed movement. Together, these results begin to uncover spatiotemporal dynamics

of cortical DA release in response to sensory stimuli and rewards, and their association during learning.

Disclosures: T. Szapary: None. **C.I. Jahn:** None. **J. Park:** None. **T. Buschman:** None.

Poster

PSTR356: Neural Circuits II

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR356.14/M24

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

Support: NIH/NIMH Grant 5R01MH132018-02
NSF Grant IOS 2137023

Title: Neural circuit mechanism underlying VTA-PFC determination of valency

Authors: *M. A. WILLIAMS[1], O. M. OGUNDELE[2];
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Abstract: Functional dichotomy of the medial prefrontal cortex (mPFC) is pertinent to the expression and suppression of executive, and other related behaviors. Although the mesocorticolimbic ventral tegmental area (VTA) that governs reward/aversion learning is reciprocally linked to the mPFC, the role of its (i.e., VTA) neuron sub-types in the dichotomous mPFC information processing are still poorly understood. Given that the valence of contexts has significant impact on their cortical encoding patterns, mapping of VTA projections to the infralimbic (IL) and prelimbic (PrL) areas of the mPFC will enhance the understanding of circuits that govern context discrimination and valence assignments. The **purpose** of this study is to create a multidimensional neuroanatomical map of VTA neural projections that innervates the IL and PrL and identify IL/PrL tracts that reach the VTA. Based on the directionality of the cell type-specific projections, modulation of VTA glutamate, dopamine, and GABA tracts in the VTA will be performed in valence-driven behavioral tasks. **Methods:** Adult C57BL/6J male and female mice will be injected with anterograde and retrograde fluorescent neural tracers that have been conjugated to a gold nanorod. The utilization of gold conjugated fluorophores will allow for both light sheet and microCT imaging of the neurons projecting to and from the VTA and PFC. Brains will be electrophoretically cleared and imaged with light sheet microscopy (LSM), and immunofluorescence detection of neuron-specific projections. Valency association will be elucidated through reward-oriented, and risk-of-punishment based tasks in a conditioned place preference test. **Results:** The anticipated results for this project are that utilizing both LSM and microCT will provide both neuron-type and sub-region-specific maps of the reciprocal connections between the VTA and IL/PrL. Thus, creating a premise for site specific targeting of these terminals in the PrL or IL during behavioral tests driven by reward acquisition (positive), punishment (negative), and the reward-risk paring. **Conclusions:** Taken together, results of this

study will elucidate the discrete roles of VTA projections in PrL and IL encoding of reward, risk, and reward-risk behavior through the modulation of anatomically mapped VTA terminals in the mPFC sub-regions.

Disclosures: M.A. Williams: None. **O.M. Ogundele:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.01/M25

Topic: G.04. Emotion

Support: NIMH R01-111604
NIAID R01-168014
NIMH R01- 121829

Title: Effects of sex hormones on gene expression in ventral hippocampus related to depression

Authors: *S. PILLAI[1], L. FURLETTI SANTIAGO[1], I. LAKIC[2], A. ROBISON[3];
[1]Michigan State Univ., East Lansing, MI; [2]Neurosci., Michigan State Univ., Haslett, MI;
[3]Physiol., Michigan State Univ., Okemos, MI

Abstract: Effect of sex hormones on gene expression in ventral hippocampus related to depression
Authors: Shruthi Pillai, Laura Furletti Santiago, Ivana Lakic, AJ Robison
Major depressive disorder (MDD) is a highly prevalent psychiatric disorder in the United States, affecting 10-15% of the population. Additionally, depression is twice as prevalent in females compared to males, but the molecular underpinnings of this discrepancy remain unknown. Chronic stress is a leading cause of depression, resulting in the dysregulation of neurochemical signaling in brain regions associated with reward and motivated behaviors, such as the ventral hippocampus (vHPC). Our lab has previously shown that baseline activity of ventral hippocampus neurons projecting to the nucleus accumbens is higher in females than males, causing susceptibility to stress-induced anhedonic behaviors (Williams et al., 2020). Additionally, vHPC is a sexually dimorphic brain region, expressing high levels of both androgen and estrogen sex hormone receptors. Sex hormones have a wide range of effects, such as activating downstream signaling cascades, gene transcription, and affecting neuronal excitability. Thus, the present studies examines: 1) whether there are sex differences in gene expression in the vHPC and brain regions associated with reward and motivated behavior; 2) the effect of sex hormones on gene expression in the vHPC and other brain regions associated with reward and motivated behavior; 3) whether testosterone administration results in increased expression of genes associated with stress resilience. Using wild type male and female 9-week-old mice, we dissected brain tissue from the vHPC, medial prefrontal cortex (mPFC), nucleus accumbens (NAc), and amygdala (AMY) to examine possible sex differences in gene expression.

In our second cohort we will gonadectomize 7-week-old male and female mice to block the production of circulating sex hormones in order to determine whether gene expression is affected by sex hormone activity. Finally, in order to find possible stress-resilient effects of testosterone, gonadectomized female mice will receive a subcutaneous implantation of the androgen dihydrotestosterone (DHT). The results of our study will help to better understand the role of sex in disorders such as depression and potentially provide possible candidate genes for future pharmaceutical targets.
Keywords: stress, depression, androgen receptor, sex differences, nucleus accumbens, ventral hippocampus

Disclosures: S. Pillai: None. **L. Furletti Santiago:** None. **I. Lakic:** None. **A. Robison:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.02/M26

Topic: G.05. Mood Disorders

Support: NIMH R01 MH112716
NIMH R01 MH128192
NIMH R21 MH113679
NARSAD Young Investigator Grant #29970

Title: Cell-type specific regulation mechanisms of depression in the nucleus accumbens

Authors: *H.-D. KIM[1], J. WEI[1], X. MA[1], H. CHO[1], Y. NGUYEN[1], A. BARNEY[1], J. PARK[2], S. QIU[1], D. FERGUSON[1];
[1]Basic Med. Sci., The Univ. of Arizona Col. of Med., Phoenix, AZ; [2]Virginia G. Piper Biodesign Ctr. for Personalized Diagnostics, Biodesign Inst., Arizona State Univ., Tempe, AZ

Abstract: Depression is the leading cause of disability and produces enormous health and economic burdens. Current treatments for depression can be partially effective, often due to the broad and non-selective action of antidepressants. Thus, there is an urgent need to design and develop novel therapeutics to treat depression. Given the heterogeneity and complexity of the brain, identification of molecular mechanisms within specific cell-types responsible for producing depression-like behaviors will advance development of therapies. In the reward circuitry, the nucleus accumbens (NAc) is a key brain region of depression pathophysiology, possibly based on differential activity of D1- or D2-medium spiny neurons (MSNs). Using a cell-type specific transcriptomics approach with RiboTag, we dissected the transcriptional profile of D1- and D2-MSNs by RNA sequencing following a mouse model of depression, chronic social defeat stress. Here we report circuit- and cell-type specific molecular targets for depression, Shisa6 and Sirt1. Shisa6 is a recently identified AMPAR component. We found increased Shisa6 expression in D1-MSNs of the NAc in susceptible mice, which enhances

excitability and depression-like behaviors. Optogenetic stimulation of the ventral tegmental area to NAc circuit, which is linked to pro-depressive effects, specifically increases Shisa6 expression just in D1-MSNs. In parallel, SIRT1, crucial for cellular metabolism and mitochondrial functions, has been identified as a gene associated with depression. RNA sequencing shows that D1-MSNs lacking functional SIRT1 exhibit altered transcriptional profiles, particularly in synaptic genes, which disrupt the balance between excitatory and inhibitory synapses, affecting GABAergic output of D1-MSNs. Taken together, these findings highlight the cell-type specific roles of Shisa6 and SIRT1 in modulating synaptic functions and suggest their potential as targets for antidepressant therapies for depression linked to circuit dysfunctions.

Disclosures: H. Kim: None. **J. Wei:** None. **X. Ma:** None. **H. Cho:** None. **Y. Nguyen:** None. **A. Barney:** None. **J. Park:** None. **S. Qiu:** None. **D. Ferguson:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.03/M27

Topic: G.05. Mood Disorders

Title: The association between depression and microRNA-20a-5p

Authors: *Y. YOSHINO[1], J. IGA[2], H. MORI[3];
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Abstract: Major depressive disorder (MDD) is a mental disorder caused by both environmental and genetic factors. Furthermore, epigenetic mechanisms may be responsible for the onset and severity of MDD. Based on previous studies that have shown microRNA (miRNA) changes in MDD subjects, we have hypothesized that miRNA could contribute to the treatment of MDD. Here, we focused on miR-20a-5p from our human data and investigated the treatment effect using the pAAV vector on mice.

Disclosures: Y. Yoshino: None. **J. Iga:** None. **H. Mori:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR357.04/M28

Topic: G.05. Mood Disorders

Support: 040630-08
SyBBURE Searle Undergraduate Research Program

Title: Investigation of nucleus accumbens calretinin interneurons

Authors: *G. BECK[1], J. ZEPEDA[2], P. ADAPA[1], B. A. GRUETER[1];
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Abstract: The nucleus accumbens (NAc) is involved in the transformation of motivation into action, and its dysfunction has been implicated in neuropsychiatric disorders such as addiction, depression, and anxiety. GABAergic interneuron populations in the NAc play a crucial role in regulating NAc function. Of the NAc GABAergic interneurons, our understanding of calretinin (CR)-expressing interneurons remains limited. Although it has been assumed that the CR-expressing neurons of the NAc are GABAergic interneurons, this has never been functionally demonstrated. We hypothesized that CR-expressing neurons are interneurons, have distinct electrophysiological properties from medium spiny neurons (MSNs) and that CR expression is recruited by psychostimulant experience. To test this, we used transgenic mouse lines, whole-cell patch techniques and qPCR. We recorded electrophysiological properties from CR-neurons and measured *Calb2* mRNA transcription and CR protein immunoreactivity post-amphetamine administration. We find that the CR(+) neurons express unique electrophysiological properties from MSNs, and that CR(+) neurons in the NAc can be separated into two neuron types defined by fast-spiking or low-threshold spiking, and that these two types of neurons also differ in their spontaneous excitatory postsynaptic current (sEPSC) frequency. Moreover, our finding that psychostimulant experience does not induce recruitment on calretinin expression suggests a stable phenotype for CR-neurons under these conditions, indicating a consistent role in regulating NAc activity across varying environments and physiological contexts. Ultimately, these studies advance our understanding of NAc circuitry and provide insights into the functional significance of CR-expressing neurons.

Disclosures: G. Beck: None. **J. Zepeda:** None. **P. Adapa:** None. **B.A. Grueter:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

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Program #/Poster #: PSTR357.05/M29

Topic: G.05. Mood Disorders

Support: Woman Scientists and Engineers R&D Career Return Support Project/WISET 2022-845
Future Source Brain Science and Technology Development Project/2E33061

Title: Mecp2 in drd2 neurons of the nucleus accumbens alleviates depression-like symptoms through rescuing synaptic function

Authors: *J. BAE[1], Y.-M. KIM[2,3], H.-I. IM[4,3];
[1]KIST, Seoul, Korea, Republic of; [2]Ctr. of Biomaterials, Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [3]Division of Biomedical Science and Technology, KIST School, University of Science and Technology (UST), Seoul, Korea, Republic of; [4]Ctr. for Brain Function, Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: MeCP2 is a transcriptional regulator that activates or represses the expression of target genes by binding on DNA. The nucleus accumbens (NAc) is one of the important areas related to reward and motivation, and is closely related to depressive-like symptoms. Moreover, dopamine D1 receptor (DRD1) and D2 receptor (DRD2)-expressing neurons, which are the majority of the NAc, differently regulate depressive-like symptoms. Here, we observed the roles of cell type-specific MeCP2 in the NAc in depressive-like symptom. We established a chronic restraint stress (CRS) model in which mice (CJ57/B6J) were detained in a restrainer for 6 hours per day for 3 weeks, and confirmed that CRS induced depressive like behaviors. Interestingly, we found the reduced MeCP2 expression only in DRD2 neurons of the NAc and not in DRD1 neurons. In addition, increasing MeCP2 in DRD2 neurons of the NAc restored CRS-induced depressive-like behavior comparable to the level of the control group. Increasing MeCP2 in DRD1 neurons did not affect depressive symptoms induced by CRS. We performed transcriptome analysis using the GeoMx Digital Spatial Profiler (DSP) to elucidate the neurological mechanism of how increased MeCP2 in DRD2 neurons of the NAc alleviates CRS-induced depression-like symptoms. Through this, we sought to identify downstream genes related to depression-like symptoms regulated by MeCP2. Increasing MeCP2 in DRD2 neurons of the NAc restored the expression levels of synaptic function-related genes altered by CRS. Additionally, we found that increasing MeCP2 in DRD2 neurons in the NAc restored the expression levels of genes altered by chronic stress in the ventral globus pallidus (VP) and dorsal striatum (DS), adjacent regions that form synapses with the NAc. Taken together, these results suggest that MeCP2 in DRD2 neurons of the NAc plays a key role in regulating CRS-induced depression-like symptoms.

Disclosures: J. Bae: None. **Y. Kim:** None. **H. Im:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR357.06/M30

Topic: G.05. Mood Disorders

Support: NIMH R01 MH128192

Title: Molecular and Circuit Mechanisms of Depression in the mPFC of Socially Defeated Mice

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Abstract: Depression is severe debilitating mental disorder that affects about 10% of Americans. While it is well established that environmental factors, such as stress, play an etiology role, the brain mechanisms, particularly the role of specific neural circuits mediating the pathogenesis of depression, remain to be elucidated. Chronic social defeat stress (cSDS) in mice is a highly relevant, validated model to study brain circuit mechanisms. cSDS has been shown to induce morphological and functional changes in multiple brain regions including the medial prefrontal cortex (mPFC), which contains heterogeneous cell types and is interconnected with other limbic brain regions such as the nucleus accumbens (NAc), ventral tegmental area, hippocampus and amygdala. Using a neuronal activity reporter mouse line, TRAP2, we found that acute (aSDS) and chronic (cSDS) social defeat stress activate distinct populations of projection neurons in the mPFC. In this study, we investigated the dysregulated gene networks in mPFC neurons activated by cSDS, exploring the dependency of these changes on SIRT1, a major genetic risk factor for depression. Utilizing an innovative combination of cSDS in TRAP2 and RiboTag mice, along with comprehensive bioinformatics analyses of RNAseq data, we have identified distinct molecular signatures that correlate with stress-induced behavioral changes. These findings underscore the potential of targeting specific neural circuits within the mPFC, offering insights into novel circuit-based therapeutic strategies that could restore synaptic homeostasis and prevent the onset of depression. Future research should focus on validating these gene networks as therapeutic targets and exploring their role in other forms of stress-related disorders, potentially broadening the impact of our findings across various types of mental illnesses.

Disclosures: A. Barney: None. **H. Kim:** None. **J. Wei:** None. **X. Ma:** None. **H. Cho:** None. **Y. Nguyen:** None. **S. Qiu:** None. **D. Ferguson:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.07/M31

Topic: G.05. Mood Disorders

Support: T32 TR004545
T32 NS082145
R01 MH053851

Title: Sex differences in the effects of manipulating the paraventricular thalamus to orbitofrontal cortex pathway during reversal learning

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Abstract: Stress-related psychiatric disorders, such as major depressive disorder and anxiety disorders, have cognitive flexibility deficits that persist even after other symptoms of these disorders go into remission. Reversal learning, a form of cognitive flexibility necessary to adapt to a changing environment, is disrupted in stress-related psychiatric disorders. The orbitofrontal cortex (OFC) mediates reversal learning, and hyperactivity in the OFC is associated with depression and obsessive-compulsive disorder in humans. Using a reward-based discrimination digging task to assess reversal learning in rodents, preliminary data using Fos immunohistochemistry showed a significant decrease in Fos in the lateral OFC following reversal learning. Further, we have previously reported that chronic stress impairs reversal learning and potentiates responses to excitatory input in the OFC, and that inducing long-term depression in the mediodorsal thalamus to OFC pathway reverses these deficits, indicating that increased activity in projections to the OFC is detrimental to reversal learning. However, the circuit-level mechanisms underlying stress-induced reversal learning deficits are not well established. The paraventricular thalamic nucleus (PVT) is highly stress responsive and is known to provide excitatory input to the OFC. Utilizing retrograde tracing from the OFC combined with ΔFosB immunohistochemistry we found that the PVT projects strongly to the OFC and this projection is repeatedly activated by chronic stress. Therefore, we next tested the hypothesis that input to the OFC from the PVT, when activated chemogenetically or by chronic stress, will disrupt reversal learning. We used an adeno-associated virus to deliver an excitatory (Gq) DREADD, an inhibitory (Gi) DREADD, or GFP control into the PVT under the control of the CaMKII promoter, and implanted guide cannulae into the lateral OFC for pathway specific in/activation. Animals received microinjections of the DREADD agonist clozapine-N-oxide (300 μM, i.c. 0.75 μL) directly preceding the reversal learning task. Activating the PVT-OFC pathway with the Gq DREADD significantly impaired reversal learning in non-stressed male rats, while inhibiting the PVT-OFC pathway with the Gi DREADD in chronically stressed animals reversed the stress-induced deficits in reversal learning only in males, with minimal or no effect of these manipulations in females. These results suggest that the PVT to OFC pathway is not as involved in the effects of stress on reversal learning in females as it is in males.

Disclosures: K. Tuite: None. **M. Girotti:** None. **D.A. Morilak:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

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Program #/Poster #: PSTR357.08/M32

Topic: G.05. Mood Disorders

Support: NIH Grant R01MH121350

Title: Sex differences in the effort-related motivational effects of the dopamine transport Inhibitor methylphenidate

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Abstract: Dopamine (DA) plays an important role in regulating behavioral activation and effort-related aspects of motivation. DA antagonism, neurotoxic depletion of nucleus accumbens DA, and the DA-depleting agent tetrabenazine (TBZ) produce a low-effort bias in rats and mice, shifting choice behavior from high-effort to low-effort alternatives. Effort-based decision-making tasks have been used to model motivational symptoms such as anergia, fatigue, and avolition, which are seen in psychiatric disorders such as depression and schizophrenia. TBZ blocks vesicular storage of DA by reversibly inhibiting the vesicular monoamine transporter type-2 (VMAT-2), and it induces depressive symptoms including fatigue and apathy in humans. Therefore, the low-effort bias induced by TBZ in rats is used to probe for the ability of drugs to improve motivational function. The effort-related effects of TBZ are reversed by administration of drugs that inhibit DA transport (DAT), but not by drugs that selectively inhibit 5-HT or norepinephrine transport. However, most of the previous research was performed in male rats. The present studies investigated the effort-related effects of the DAT inhibitor methylphenidate in male and female rats. The first group of studies employed the concurrent fixed ratio 5 (FR5)/chow feeding choice task. TBZ shifts choice behavior, decreasing lever pressing but increasing chow intake in a dose range of 0.25-1.0 mg/kg IP in male rats, while a higher dose is needed to achieve the same effect in females (2.0 mg/kg IP). Co-administration of the DA transport inhibitor methylphenidate (1.0-4.0 mg/kg IP) reversed the effort-related effects of 1.0 mg/kg TBZ in male rats, and was also effective in females injected with the 2.0 mg/kg dose of TBZ. However, the actions of methylphenidate were characterized by different dose-related characteristics across sexes, with the effect being more potent in females. There also were sex differences in the effects of methylphenidate (1.0-4.0 mg/kg IP) on progressive ratio (PROG) lever pressing, and on performance of a PROG/chow feeding choice task. Female rats showed little effect in the dose range tested, while males were responsive to the ability of methylphenidate to enhance the selection of high-effort PROG responding. Investigating sex differences in the pharmacology and neurochemistry of effort-based choice may lead to a greater understanding of the role of sex as a factor in motivational dysfunctions in humans, and may contribute to the development of treatments for effort-related psychiatric symptoms.

Disclosures: J.D. Salamone: None. **A. Ecevitoglu:** None. **G.A. Edelstein:** None. **P. Matas Navarro:** None. **M. Correa:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.09/M33

Topic: G.04. Emotion

Support: European Union's Horizon 2020 program: Marie Skłodowska-Curie Innovative Training Network (956414)

Title: The role of cerebellar endocannabinoid CB1 receptors in anxiety and decision making

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Abstract: Recently, the cerebellum has gained attention for its role in the regulation of emotional responses, including reward and fear-related behaviours. However, the involvement of the cerebellum in the regulation of anxiety remains poorly understood. An important neuromodulatory system involved in anxiety is the endocannabinoid system. The cerebellum is one of the brain regions with the highest expression of the cannabinoid receptor 1 (CB1), but very little is known about its contributions to cerebellar function. The present project studied the behavioural effects of blocking endocannabinoid signalling in the cerebellar vermis. In Sprague-Dawley rats (n=24, 58% female), a cannula was chronically implanted into the cerebellar vermis and the CB1 receptor antagonist NESS0327 was infused into the cerebellum prior to behavioural testing in an elevated plus maze (EPM) and open field arena. A significant reduction in time spent in the open arms of the EPM was observed following infusion of drug compared to vehicle ($p = 0.015$), suggesting an anxiogenic effect of blocking CB1 receptor signalling in the cerebellar vermis. However, this effect may also be due to an increase in the time spent at the entrance of the closed arms (which, alongside the central area of EPM, are considered to be the decision-making points of the maze $p = 0.0099$). By comparison, no difference was found between drug and vehicle treatment in the time spent in the centre of the Open Field ($p > 0.05$), suggesting an absence of anxiogenic effects in this behavioural context. Experiments are currently underway to record the effects of agonising and antagonising CB1 receptors on local field potential activity in the cerebellum during EPM testing. In summary, our results to date suggest the consequences of blocking CB1 receptor signalling in the vermal cerebellar cortex in rats are behaviourally specific, and may relate more to decision making than anxiety per se.

Disclosures: F. Senovilla Sanz: None. **J. Pickford:** None. **R. Apps:** None. **C.L. Lawrenson:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.10/M34

Topic: G.05. Mood Disorders

Support: NSF Career 2235858

Title: Effect of alcohol on natural cost benefit decision making

Authors: *A. Y. MACIAS[1], R. IBANEZ ALCALA[1], S. BATSON[1], A. SALCIDO[1], K. NEGISHI[2], A. RAMIREZ[3], L. E. O'DELL[4], T. M. MOSCHAK[5], K. GOOSENS[6], A. FRIEDMAN[7];
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Abstract: Every day, we navigate complex decisions involving a series of rewards and costs. This decision making (DM) process can be altered by internal or external factors, such as alcohol. Previous research shows that both acute and chronic alcohol consumption can result in notable shifts in DM, impacting decisions beyond those related to alcohol. Moreover, individual differences in alcohol consumption, including levels of intake and susceptibility to its effects, highlight the intricate interplay of biological and behavioral factors in alcohol consumption susceptibility and progression.To address this, we employed our behavioral task battery, RECORD (Linking Group: AsparagusCerise), which delivers a distinct reward (sucrose: 0.5, 2, 5, 9%), paired with one of two costs: 15 lux (low cost) and 320 lux (high cost) light. To establish a DM tradeoff, we inverted alcohol concentration with existing sucrose concentrations (9% SC + 1% alc, 5% SC + 4% alc, 2% SC + 10% alc, 0.5% SC + 20% alc).In our study, male (n=11) and female (n=12) rats underwent 9 weeks of training in high and low-cost, cost-benefit tasks. Behavioral features (approach rate, approach time, number of high-speed runs, distance travelled, number of stopping points) were evaluated across initial (1-3 wks) and late (6-9 wks) alcohol task. Approach rate was significantly greater in alcohol task compared to control. From wk. 9, significant differences in concentration acceptance were observed. In late task, alcohol consumption became significant alluding to an exposure dependent preferential acceptance of alcohol.Significant differences in sex performance were apparent, where females approached paired offers more than males in control and alcohol groups. Control and alcohol DM patterns are both modeled by sigmoidal shaped functions (SSF), where low rewards (0.5 and 2% SC) result in decreased approaches and high rewards (5 and 9% SC) result in increased approaches. However, when cluster analysis was performed, the proportion of cluster participation in baseline groups greatly varied when compared to alcohol. Considering changes in Euclidean distances between clusters before and after alcohol consumption, we identify individual variances in DM. Rats vulnerable to alcohol consumption displayed greater variations in cluster participation, where resilient rats deviated with less intensity. These shifts in DM patterns allude to varying behavioral DM strategies, which can be altered between individuals and sexes in a context dependent manner. RECORD presents a tool for understanding and potentially predicting individual differences in DM, as well as for measuring the effects of alcohol on these DM processes.

Disclosures: A.Y. Macias: None. **R. Ibanez Alcala:** None. **S. Batson:** None. **A. Salcido:** None. **K. Negishi:** None. **A. Ramirez:** None. **L.E. O'Dell:** None. **T.M. Moschak:** None. **K. Goosens:** None. **A. Friedman:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.11/M35

Topic: G.05. Mood Disorders

Support: NSF Career 2235858
NIGMS 1T32GM144919

Title: Effect of oxycodone on natural cost benefit decision making

Authors: *S. A. BATSON[1], R. IBANEZ ALCALA[2], A. SALCIDO[2], A. A. MACIAS[2], K. NEGISHI[4], A. RAMIREZ[2], L. E. O'DELL[5], T. M. MOSCHAK[2], K. GOOSENS[6], A. FRIEDMAN[3];
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Abstract: Oxycodone (oxy) is a drug of abuse, contributing to the increase of opioid related overdoses. A commonly accepted dogma is that oxy use results in altered drug related decision making (DM). Unclear, however, is oxy's impact on non-drug related DM before, during (self-administration), and after (abstinence) use. To address this, we utilized an operant chamber where rats (n=33) spent 6hrs/day for 14 days self-administering (self-admin) oxy. Daily, following self-admin, rats underwent a modified cost-reward task (RECORD), used in food deprivation and alcohol validation efforts, where four rewards (9, 5, 2, and 0.5% sucrose) are paired with costs (15 and 320 lux light), limited in this study to 280 lux due to hypersensitivity. Prior to use, 95% of DM is represented by a sigmoid shaped function (SSF), where low offer response aligns with low rewards (0.5 and 2% sucrose) and high offer response aligns with high rewards (5 and 9% sucrose). During use, DM patterns deviated, and approach rates flattened alluding to impaired DM and reward hyposensitivity. The number of sessions now represented by SSF's dropped to 45%. Cluster analysis unveiled patterns in self-admin DM strategies, with notable alteration in the distance travelled (DT) cluster. Evaluating vulnerable populations, shifts in cluster participation across 6 behavioral features (DT, approach time, approach rate, number of stopping points, number of high-speed runs, proportion of trial outside all reward zones) and Euclidean distances between clusters is altered during oxy use. When in a 30-day abstinence period, flattened approach rates persisted while DT in the oxy population increased. The number of sessions represented as SSF's increased to 55%, demonstrating a return to pre-oxy levels. Determining if sex plays a role in oxycodone vulnerability and resilience, the same behavioral parameters were evaluated in both sexes. Consistent with literature, females (n=5) consumed more oxy (average 5.6mg/session) than males (n=5, average 2.7mg/session) resulting in reduced SSF's. During drug use, significantly different approach times between sexes were observed. Opposing effects due to sex where also observed in DT, number of stopping points, and number of high-speed runs. This strong deviation from typical DM marks female rats as vulnerable to the effects of oxy use. Comparing sexes following abstinence, all features apart from DT, returned to pre-oxy levels. Despite, on average, most DM parameters returning to baseline following

extended absence of oxy, few demonstrate continued deviation on the individual level further exemplifying the need to explore the implications of drug use on non-drug related DM.

Disclosures: S.A. Batson: None. **R. Ibanez Alcala:** None. **A. Salcido:** None. **A.A. Macias:** None. **K. Negishi:** None. **A. Ramirez:** None. **L.E. O'Dell:** None. **T.M. Moschak:** None. **K. Goosens:** None. **A. Friedman:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.12/M36

Topic: G.05. Mood Disorders

Support: NSF 2235858

Title: Record: a high-throughput system for complex naturalistic decision-making in rodents

Authors: *R. J. IBÁÑEZ ALCALÁ[1], A. SALCIDO[1], S. BATSON[1], A. MACIAS[1], K. NEGISHI[3], A. RAMIREZ[4], J. AGUIRRE[1], L. E. O'DELL[2], T. M. MOSCHAK[1], K. A. GOOSENS[5], A. FRIEDMAN[1];
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Abstract: Decision-making (DM) is a human-relevant behaviour that can be studied translationally using laboratory animals, however doing so poses many challenges. To tackle these challenges, we designed an automated, high throughput framework for the study of cost benefit (CB) DM in rodents at multiple levels of cost and reward. The REward-COst in Rodent Decision-making (RECORD) system consists of 3D printed modular arenas, custom electronic hardware, and software for databasing and data analysis. RECORD uses spatiotemporal tracking and many reward and cost combinations (sucrose concentration SC and light intensity LI) to create a vast DM dataset. Our software suite processes the data into various metrics for classification and modelling, namely psychometric functions, behavioural features, and CB integration maps.
We designed DM tasks which leverage RECORD's ability to combine multiple levels of cost (varied between 9 and 320 lux of blue light) and reward (0.5, 2, 5, and 9% SC). One cost-reward pair (offer) is presented at a time, then the animal is tracked to determine whether it approached the offer before dispensing it. In validations with a rat model (n = 12 female, n = 11 male, Long-Evans), rats approached higher SC more and avoided the higher LI. All metrics were successfully created from the group of rodents' data without the need for food deprivation (FD), a common motivator.
To test behavioural DM bias caused by FD, we first recorded rats (n = 22) performing a set of high and low-cost tasks without FD. Then, we reduced their regular meals and weighed them daily for 3 weeks until we observed a weight reduction of 0% - 20% of their initial weight. Both

tasks were performed again and the results were compared against no FD data. This resulted in increased approach rates for higher SC and alteration of nearly all behavioural features. The relationship between reward and cost changed, reflected in CB integrations, indicating a desensitisation to cost. Similarly, we tested the effects of oxycodone and alcohol, then compared the generated data against a control group, and again found altered DM patterns. Calcium (Ca2+) imaging (n = 5 rats) using Inscopix's nVoke miniscope system revealed that Ca2+ activity in the anterior dorsomedial striatum increased during high-cost tasks.
RECORD's feature set allows its data to be distilled into a neuroeconomic model to understand animals' DM patterns through principles like subjective value or choice utility. It enables comparisons between multiple experiments to determine the effect of a variable, context, or condition. It is a powerful and sensitive tool to study DM in animals and facilitates translational studies on psychiatric disorders.

Disclosures: R.J. Ibáñez Alcalá: None. **A. Salcido:** None. **S. Batson:** None. **A. Macias:** None. **K. Negishi:** None. **A. Ramirez:** None. **J. Aguirre:** None. **L.E. O'Dell:** None. **T.M. Moschak:** None. **K.A. Goosens:** None. **A. Friedman:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR357.13/M37

Topic: G.05. Mood Disorders

Title: Effects of escitalopram on amphetamine withdrawal in rats

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Abstract: Behavioral and physiological symptoms during early withdrawal of psychostimulants are thought to resemble symptoms of depression in humans. Previously, we reported that rats had reduced locomotor activity 12-24 hours post-drug administration of psychostimulants or opioids. Following psychostimulants, this sign of withdrawal was completely blocked by a dopamine D1 antagonist and partially blocked by a kappa opioid antagonist. The present study examined the effects of an antidepressant on amphetamine withdrawal in rats. Female Wistar rats received a series of tests during which locomotor activity was monitored in an open field for 24 hours after each treatment. Near light-onset of Test Day 1, animals were treated with saline. On Test Day 4, each animal received drug treatment. Effects produced by saline and drug treatments were compared. Drug treatments included amphetamine (2mg/kg s.c.) or amphetamine + escitalopram (2.5mg, 5mg, or 10mg s.c., given 15 minutes after amphetamine). Escitalopram is a selective serotonin reuptake inhibitor (SSRI), which is commonly used to treat major depression. Consistent with our previous report, amphetamine reliably produced withdrawal. Escitalopram affected amphetamine-induced withdrawal: the low dose of escitalopram prevented the

amphetamine-induced reduction in activity from 12-24 hours, the moderate dose showed a non-significant trend, whereas a high dose failed to do so. During the first 3 hours following treatment, escitalopram attenuated the locomotor response to amphetamine. Interestingly, elevated activity was seen beginning about 3 hours following amphetamine + escitalopram treatment, and activity remained elevated for approximately 5-6 hours in a manner that was escitalopram-dose dependent. Our data suggest that acute withdrawal from amphetamine and major depression may share similar mechanisms, and that investigating amphetamine acute withdrawal might provide insight into the mechanistic determinants of depression.

Disclosures: I.M. White: None. **B.A. Heidenreich:** None. **W. White:** None.

Poster

PSTR357: Depression and Decision Making: Neural Mechanisms

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Program #/Poster #: PSTR357.14/M38

Topic: G.05. Mood Disorders

Support: University of Connecticut Research Foundation
University of Connecticut Holster Scholar Program

Title: The Triple Reuptake Inhibitor Diclofensine Reverses the Low-effort Bias Induced by the Dopamine Depleting Agent Tetrabenazine: Comparisons with Catecholamine and 5-HT Transport Inhibitors

Authors: *G. EDELSTEIN[1], A. GOLDHAMER[2], A. ECEVITOGLU[3], S. PAPANIKOLAOU[1], M. MITOLA[1], K. BEARD[1], P. MATAS NAVARRO[4], A. MARTÍNEZ VERDÚ[5], R. OLIVARES-GARCÍA[6], M. CORREA[7], J. D. SALAMONE[8];
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Abstract: Monoamine transport inhibitors are the most common treatments for depression, but across various drugs there are many different profiles of action on distinct monoamine transport proteins. Although inhibitors of serotonin transport (SERT) are the most widely prescribed antidepressants, evidence indicates that these drugs are limited in their effectiveness at treating motivational dysfunctions such as anergia and fatigue. In contrast, drugs that act on the catecholamines dopamine (DA) and norepinephrine (NE), such as bupropion, are reported to be more effective at treating motivational dysfunction. Current antidepressant development efforts include the evaluation of triple reuptake inhibitors (TRIs). TRIs exert their effects by inhibiting the DA transporter (DAT), NE transporter (NET) and SERT. However, the order of relative binding affinities that will produce the greatest therapeutic effect on motivational dysfunction is

uncertain. Based on previous research, it is hypothesized that TRIs that have a DAT>NET>SERT order of affinity would have an optimal therapeutic potential for addressing effort-related motivational symptoms. Rodent tests of effort-based choice are used as models for assessing the effort-related motivational effects of drugs, including antidepressants. The present studies assessed the ability of various drugs that inhibit monoamine transporters for their ability to reverse the low-effort bias induced by the VMAT-2 inhibitor and DA depleting agent tetrabenazine (TBZ). In rats tested on the fixed ratio (FR) 5/chow feeding choice task, TBZ shifts choice, reducing lever pressing but increasing chow intake. The TRI diclofensine was tested for its ability to attenuate TBZ-induced shifts in behavior on the FR5/chow feeding choice task, due to having its highest affinity at DAT. Diclofensine induced a significant but partial reversal of the suppression of the high-effort lever pressing induced by TBZ. Consistent with previous studies, the DAT/NET inhibitor bupropion reversed the effects of TBZ. The NET/DAT inhibitor nomifensine also partially reversed the lever pressing suppression induced by TBZ, but the NET inhibitor atomoxetine and the NET/SERT inhibitor duloxetine were ineffective. Microdialysis methods are being used to assess the neurochemical effects of these different monoamine uptake inhibitors to compare to the behavioral effects produced by each compound. Taken together with previous studies, the present results indicate that actions on DAT are critical for exerting pro-motivational effects in models of effort-based choice.

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Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.01/M39

Topic: G.03. Motivation

Support: ARC FT230100656
ARC FT220100294
ARC DP180102383
ARC DP200100234

Title: Dopamine D2/D3 blockade modulates the relationship between reward and movement vigour

Authors: H. JARVIS, M. A. BELLGROVE, J. P. COXON, ***T. CHONG**;
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Abstract: Humans and other animals tend to move faster in pursuit of larger rewards. This process of action invigoration is shaped by dopamine, which encodes both the value of available rewards in the environment, and also the reward prediction errors (RPEs) that drive learning.

Importantly, the question of whether vigour is shaped primarily by the rewards themselves or RPEs is unresolved. In this study, we aimed to: (1) compare the relative contribution of reward and RPE to the vigour of motor actions; and (2) determine the degree to which the relationship between reward/RPE and vigour relies on intact dopamine D2/D3 signalling. Healthy young adults were randomised to receive either high-dose sulpiride (which acts as a selective post-synaptic D2/D3 receptor antagonist) or placebo in a double-blind design. Participants then performed a novel reinforcement learning task, in which they received trial-by-trial reward feedback designed to generate parallel reward and RPE signals. After a variable delay following feedback, an action cue prompted participants to execute a speeded motor response to increase their winnings using a pair of hand-held dynamometers. We quantified the vigour of the speeded response with two independent metrics: (1) reaction times, and (2) the time-to-peak force. Across all participants (regardless of drug), both reaction time and time-to-peak force were more sensitive to reward than the magnitude of the RPE. However, sulpiride had distinct effects on each vigour parameter - it slowed reaction times only when rewards were small, but more generally delayed the time-to-peak force regardless of reward. Computational models of vigour revealed that these effects of sulpiride were driven by an attenuation of reward-guided behaviour, against the background of an overall reduction in the capacity for rapid force generation. Together, these data emphasise the importance of rewards over RPEs in shaping movement vigour, and highlight the complex role of the dopamine D2/D3 receptor in both maintaining this relationship, and more broadly facilitating the execution of motor plans.

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Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

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Program #/Poster #: PSTR358.02/M40

Topic: G.03. Motivation

Support: Oxford MRC Doctoral Training Partnership

Title: Mesolimbic dopamine reports reward rate and task-engagement in freely moving mice

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Abstract: Dopamine is a key monoamine neurotransmitter involved in reward-guided flexible decision-making. Several studies indicate that fast, transient dopamine release in the nucleus accumbens core (NAc) carries reward-prediction error signals. However, accumulating evidence suggests that slower, sustained changes in dopamine may transmit distinct information about recent reward history. Nonetheless, it is yet to be determined what precise reward-related information is conveyed by sustained dopamine signals, and how these may influence task

performance and engagement. To investigate these issues, we delivered the dopamine sensor dLight1.1 into NAc, as well as the red-shifted channelrhodopsin ChrimsonR bilaterally in the ventral tegmental area, to DAT-Cre mice (N=7, 4 females, 10 weeks old). We then measured dopamine-dependent fluorescence changes using fibre photometry as freely-moving mice performed a 2-armed bandit task which required them to initiate each trial in a central poke and then choose between left and right pokes to gain rewards. To modulate the richness of the environment in different ways, sessions were divided into blocks of variable length (15-25 trials) and across blocks, one of three possible changes occurred: (i) the reward probabilities were changed between high (0.9/0.5) or low (0.5/0.1) pairs; (ii) the inter-trial interval (ITI) was changed between short (2-4s) or long (7-9s); or (iii) the optimal side was reversed. Mice's behaviour tracked block richness: they had the highest reward collection rate and the shortest latency to initiate the next trial in short ITI, high reward probability blocks. Sustained NAc dopamine levels were significantly higher both when rewards became available at higher frequency (short ITI) and with a higher likelihood (0.9/0.5 probability blocks), irrespective of previous outcome. Additionally, during periods of higher reward yield when sustained dopamine levels were high, mice were less likely to disengage from performing the task. Notably, not only transitions to disengagement but also transitions to engagement were preceded by low tonic dopamine, suggesting tonic dopamine might modulate the probability of any behavioural transition. However, the two types of transitions could be distinguished by a rapid dopamine increase aligned around transitions from disengaged to engaged states. Together, these findings clarify the role of sustained mesolimbic dopamine in reporting reward rate and modulating animals' willingness to engage with the task, and suggest how transient dopamine activity may be involved in orchestrating motivation to re-engage with reward-oriented behaviour.

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Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.03/N1

Topic: G.03. Motivation

Support: PhD funding by Science Foundation Ireland under Grant number 18/CRT/6183

Title: Structural MRI correlates of individual differences in subclinical apathy and effort-based decision making

Authors: *N. TRINH[1], P. VASSILIADIS[2], L. DRICOT[3], J. DUQUE[4], T. WARD[5], G. DEROSIERE[6];
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Belgium; [4]UCLouvain, Brussels, Belgium; [5]Insight SFI Res. Ctr. for Data Analytics, Dublin City Univ., Dublin, Ireland; [6]Ctr. de Recherche en Neurosci. de Lyon, Bron, France

Abstract: Effort-based decision making is essential for goal pursuit and disrupted in apathy. Apathy is highly prevalent across almost all psychiatric and neurological disorders. Even in otherwise healthy people, there is a large inter-individual variability in apathy, with some individuals exhibiting high apathy scores, though below the clinical threshold, indicative of what is known as subclinical apathy. Despite its significance, the neural underpinnings of individual differences in subclinical apathy and effort-based decision making remain elusive. In this study, we addressed this gap by investigating 50 healthy human subjects through comprehensive neuropsychological assessments of apathy, depression and anhedonia. Participants also performed a task which required them to choose between exerting varying levels of physical effort for monetary rewards; computational modeling of acceptance rates in this effort-based decision-making task enabled quantification of subjective effort and reward valuation in each individual. Structural magnetic resonance imaging data (MRI, sequence: 3d T1 MPRAGE) were collected for each participant. The whole brain was analyzed and volumetrically segmented by employing FreeSurfer using an array of automated sequences. The Brainnetome atlas (246 regions of interest) was used to map parcellation (cortex) and segmentation (subcortex) labels to subjects. We utilized LASSO regression, a data-driven approach, to identify specific brain regions associated with inter-individual differences in subclinical apathy scores, as well as effort and reward valuation. Our analyses reveal significant negative correlations between subclinical apathy scores and gray matter volumes of frontal areas involved in action execution, including the frontal eye field and the premotor cortex. Additionally, areas involved in speech production, including the ventrolateral part of the inferior temporal gyrus, also show significant negative correlations. Atrophy in these structures may lead to decreased engagement in physical actions, including eye movements, body movements, and speech. Current analyses focus on the relationship between gray matter volumes and subjective effort and reward valuation parameters, as obtained using computational modelling of decision behaviour in the task.

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Poster

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Topic: G.03. Motivation

Support: NIH Grant R01DA035943

Title: Dysregulation of mesolimbic dopamine signaling negative reward prediction error and its impact on behavioral flexibility

Authors: *R. MAGNARD[1], Y. CHENG[1], Y. VANDAELE[2], P. H. JANAK[1,3];
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Abstract: Midbrain dopamine (DA) neurons are proposed to convey the difference between anticipated and received rewards, serving as a dynamic teaching signal, necessary for rapid adaptation to environmental changes. We previously demonstrated the importance of VTA DA signaling during proximal reward predictive cues for driving automaticity in action sequence learning. This was shown through testing rats in two operant tasks: lever insertion fixed-ratio 5 (LI5) and lever retraction fixed-ratio 5 (LR5). In LI5, where the lever serves as the distal cue initiating the lever press sequence, performance is goal-directed. In LR5, where the lever signals sequence completion and reward delivery, performance is faster, less variable, and more habitual. Here, we extend this work by probing behavioral flexibility and its DA correlates in these two procedures when rats are challenged by a reward omission test. In this test, rats must restrain from pressing the lever for 20s to receive reward (sucrose 20%). Completion of the five lever press ratio results in reward omission. During the omission test, we recorded VTA DA neuron activity and NAc Core DA release via fiber photometry. TH-Cre or WT rats were infused with a Cre-dependent GCaMP6f in VTA (LI5: 3 males, 5 females; LR5: 5 males, 5 females) or with the DA sensor dlight1.2 in NAc Core (LI5: 3 males, 5 females; LR5: 5 males, 5 females). Substantial task differences were observed. When reward delivery was no longer contingent on lever presses, LR5-trained rats displayed a higher number of ratios completed, faster execution speeds, and a greater likelihood of lever pressing upon unexpected reward delivery, compared to LI5-trained rats (all p's<.01), demonstrating a lack of within-session behavioral flexibility. We observed distinct changes in DA signaling consistent with task differences in behavior. Both VTA and NAc Core DA signaling revealed a peak at port entry for both groups following ratio completion and reward omission, but after 1s inside the magazine, while LI5 rats displayed a DA dip, indicating awareness of the absent reward, LR5 rats maintained baseline DA activity, suggesting a negative RPE deficit (LI5 vs LR5, AUC p<.01). No difference was observed between groups for unexpected reward delivery. These results suggest that VTA/NAc Core DA is important for normal behavioral flexibility under changing reward in goal-directed behavior. In contrast, the observation of blunted DA negative RPE signals after expected reward omission in a more habitual rats suggests lack of flexibility is related to loss of DA RPE-like dynamics.

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Poster

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Topic: G.03. Motivation

Support: NIH Grant MH119086

Title: Behavioral determinants underlying expectation-dependent effort preferences

Authors: *A. KIM[1,2], V. S. CHIB[1,2];
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Abstract: When deciding how much effort to put into work, individuals consider various factors such as expected payoff, fatigue levels, and attitudes towards the loss and risk associated with resulting incentives. While previous studies have examined these factors individually, their combined impact on decisions to exert effort remains unclear. We investigated how expected payoff, fatigue, and aversion to loss and risk shape individuals' preferences regarding effort expenditure. Thirty young participants completed an experiment comprised of (1) a fatigue questionnaire to assess fatigue levels, (2) an incentive preference task to assess loss and risk aversion for monetary rewards, and (3) a reward-based effort task to probe the influence of expected payoffs on effort preferences. During each reward-based effort trial, we presented participants with a risky option that could yield either fixed monetary payment, independent of their effort exertion, or payment based on the amount of effort exerted, called piece-rate payment. Each of these options had an equal probability of occurring. The piece-rate payment was either Low (maximum exertion yielded $2) or High (maximum exertion yielded $6), where the maximum payment was lower or higher, respectively than the maximum fixed payment ($4). We manipulated the fixed payment and piece-rate condition to vary reward expectations. The payment was revealed after individuals had a chance to exert effort. We found that participants exerted greater effort under the High piece-rate condition compared to the Low piece-rate condition (linear mixed-effects model, $t(321) = -5.31$, $p < 0.001$). Moreover, overall effort increased with higher fixed payment ($t(321) = 2.41$, $p = 0.016$), but there was no interaction between the piece-rate condition and fixed payment. Interestingly, individuals experiencing heightened cognitive fatigue exhibited riskier effort-related behaviors (i.e., reduced effort exertion) as reward expectations increased, particularly in the High piece-rate condition (robust regression, $p = 0.022$), but not in the Low piece-rate condition. Furthermore, risk aversion partially mediated the impact of fatigue on effort preferences based on reward expectations under the High piece-rate condition ($p = 0.044$). Specifically, more cognitively fatigued individuals exhibited greater risk aversion, leading to a preference for less effort despite increasing reward expectations (i.e., riskier effort-related behavior). Overall, these results may highlight the behavioral factors influencing individuals' effort preferences, including expectations of increasing incentives, cognitive fatigue, and risk aversion.

Disclosures: A. Kim: None. **V.S. Chib:** None.

Poster

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Topic: G.03. Motivation

Support: NIH Grant 5RO1NS123396

Title: Parsing effort costs with a novel effort-based decision making task

Authors: *G. A. ELIAS, D. B. HEADLEY;
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Abstract: When pursuing a reward, we often balance the work required to obtain it with its desirability. Known as effort-based decision making, its neural basis is extensively investigated in both humans and animals. Studies in rodents have relied upon task paradigms that present two options, one being low effort/low reward and the other high effort/high reward. For instance, climbing a hurdle to obtain multiple food pellets, or repeated lever pressing for a favored treat. These tasks treat effort as a monolithic cost, which is not amenable to understanding the multiple factors that comprise effort. A task that isolates distinct dimensions of work, principally the level of physical exertion as well as the duration of it, would allow better characterization of the neural coding of effort and the functional specialization of brain regions supporting effort-based decision making. With that in mind, we developed a novel rodent effort-based decision-making task. In this task, rats choose between turning a wheel for a large reward or pressing a lever for a small one. Trials are signaled by a steady 1kHz tone to cue the rat to begin wheel turning. Thereafter a pulsed tone (125ms pips) increases in frequency while the rat rotates the wheel. A large reward is delivered once the tone pips reach 48kHz. Alternatively, the rat can disengage from the wheel early and lever press for a small reward. Across trials, work costs are varied in terms of force required to rotate the wheel (0.01, 0.04 or 0.08 Nm torque) and the duration the trial (3, 6 or 12s; signaled by the rate at which tone pips increase in frequency) allowing parsing of their respective contributions to effort. We find that rats trained on this task display significant effort discounting. As work costs increase, rats increasingly prefer the smaller lever reward. This shift in preference arises from a choice based discounting effect, not increased failure rate due to the increasing work requirements. Comparing wheel completion rates under forced (only wheel accessible) and free (both wheel and lever accessible) choice conditions using a survival analysis revealed a significantly more uniform distribution of wheel quits in the forced choice condition. In the free choice condition, quit times were disproportionately higher within 2s of trial start compared to the rest of the trial. This suggests that rats rapidly (within ~2s) evaluated and weighed the relative cost and benefits of engaging with the wheel when provided an alternative reward source. These results show that our task replicates basic economic principles and is well suited for probing the neural coding of effort.

Disclosures: G.A. Elias: None. **D.B. Headley:** None.

Poster

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Program #/Poster #: PSTR358.07/N5

Topic: G.03. Motivation

Title: Cross-validation of two measures of sign-tracking in humans

Authors: *M. POTTS[1], J. STAMBAUGH[2], M. V. CHERKASOVA[3];
[1]Psychology - Behavioral Neurosci., [3]Psychology, [2]West Virginia Univ., Morgantown, WV

Abstract: Animals vary in the degree to which they attribute incentive salience to reward-predictive cues. In Pavlovian conditioning, two behavioral phenotypes emerge: *goal-tracking*, in which animals approach the site of the reward, and *sign-tracking*, in which animals approach and interact with the conditioned stimulus as if it is rewarding. Sign- and goal-tracking conditioned responses have been differentially associated with addiction-relevant behavioral features in animal models and have been proposed to represent markers of addiction vulnerability. Initial evidence suggests that similar phenotypes may be identified in humans and are possibly related to addiction proneness. However, extant human studies have relied on different paradigms for measuring sign-tracking, and the translational validity of these phenotypes remains an area of active research. We cross-validated two major methods that have been used to measure sign-tracking in humans: 1) visual attention to reward-predictive conditioned stimuli during Pavlovian conditioning in the Pavlovian-to-Instrumental Transfer (PIT) paradigm, and 2) attentional capture to task-irrelevant reward-associated distractors in the Value-Modulated Attentional Capture (VMAC) visual search task. Nine human participants completed a PIT paradigm, in which sign-tracking was quantified as relative duration of eye gaze fixations on a reward-predictive cue versus the location of impending reward delivery, followed by a VMAC task, in which sign-tracking was measured as increases in latency to saccade to a target in the presence of reward-predictive distractors. Although our research is ongoing, preliminary data suggests that phenotype classification according to PIT does not align with classification in VMAC, suggesting that these tasks may be assessing distinct constructs.

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Poster

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Topic: G.03. Motivation

Support: NIH Grant 5R01MH132018-02
NSF IOS 2137023

Title: VTA Dopamine modulation of reward context discrimination.

Authors: *R. FALLAHSAFA[1], O. M. OGUNDELE[2];
[1]Comparative Biomed. Sci., Louisiana State Univ., Baton Rouge, LA; [2]Louisiana State Univ., Baton Rouge, LA

Abstract: Neurons in the ventral tegmental area (VTA) are a diverse population of cells that play a critical role in the regulation of reward, aversion, motivation, and reinforcement learning. Notably, the VTA-amygdala dopaminergic pathway is involved in regulating motivation and decision-making processes. Activation of these projections can modulate approach or avoidance behaviors based on the perceived value of rewards or threats. However, how VTA-amygdala projections to midbrain regions that drive reward-aversion learning contribute to determining the weight of positive and negative valanced contexts - e.g., reward - is still poorly understood. The current study deploys *cre-lox* recombination and chemogenetic modulation methods to target VTA Dopamine neurons in a conditioned place preference test where TH^{Cre} mice made a ranked choice between two positively valanced contexts (sucrose and sucrose/EtOH). In the learning phase, mice were exposed to sucrose in two contexts that differed in spatial location, visual cues, tactile cues, and odor (vinegar or none). Each mouse preferred one context to the other while obtaining the sucrose reward. As such, in the conditioning phase mice choose between sucrose on the preferred side, and sucrose/alcohol on the non-preferred side. Results of the baseline testing phase showed that mice spent more time in sucrose/alcohol side, compared with sucrose-only. However, selective excitation of VTA Dopamine neurons during the conditioning phase alters the ranked choice between the two types of reward. Consequently, the propensity for exploring contexts containing sucrose or sucrose/alcohol was comparable with VTA Dopamine stimulation. We conclude that activation of VTA dopamine neurons during the conditioning phase of reward-choice and context discrimination tasks alter choice and context discrimination outcomes.

Disclosures: R. Fallahsafa: None. **O.M. Ogundele:** None.

Poster

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Topic: G.03. Motivation

Support: NSF IOS 2137023
NIH/NIMH R01MH132018-02

Title: Ventral Tegmental Area glutamate projections guide hippocampal encoding of space and contexts.

Authors: *S. SINZA[1], O. M. OGUNDELE[2];
[1]Comparative Biomed. Sci., Louisiana State Univ., Baton Rogue, LA; [2]Louisiana State Univ., Baton Rouge, LA

Abstract: Reciprocal connections between the mesocorticolimbic ventral tegmental area and hippocampus constitute an anatomical loop that governs aspects of learning and processing of information for long-term cortical storage. Although the VTA contains diverse neuron types, the

dopamine-releasing types have been studied extensively, and their functions are defined in reward/aversion, cognition, and other complex behaviors. The role of the excitatory glutamate groups is still emerging with recent studies examining their role in context learning, discrimination, and valency detection in contexts. The goal of the current study is to determine how VTA glutamate innervation of the ventral hippocampus directs CA1 encoding of spatial learning that is contextualized by reward placement. This is to test the hypothesis that VTA glutamate neurons guide CA1 neurons to determine the value of spatial contexts based on the probability of obtaining a reward. To test the functional implication of VTA glutamate innervation of the vCA1, light controllable excitatory opsin was expressed in VTA glutamate neurons by stereotaxic injection of AAV-DIO-ChR2 into the VTA of *Vglut2*^{cre} mice (n=6). To assess the VTA-vCA1 glutamate tract in freely behaving mice, a fiber-optic cannula was positioned in the vCA1 (close to the VTA) while recording neural probe shanks were placed in the dCA1 (dorsal CA1). A baseline T maze test was performed without stimulation. After a washout period, the behavioral task was performed with optogenetic activation of the VTA glutamate projections when a correct choice was made to obtain a sucrose reward. Behavioral tracking and hardware control TTL systems synchronized behavioral task events, dCA1 recording, and vCA1 photo-modulation. The outcomes of this experiment demonstrate the role of the VTA-vCA1 glutamate tract in spatial learning events driven by reward. Furthermore, firing rate and correlogram analysis will be performed to examine the role of this tract in CA1 encoding of spatial contexts when a reward is presented or omitted. Together, a combination of CA1 recording and VTA-vCA1 glutamate tract modulation will provide a premise for assessing the role of VTA glutamate neurons in hippocampal encoding of space and discrimination of context based on value assignment.

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Poster

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Topic: G.03. Motivation

Support: Lundbeck Foundation R359-2020-2301
Lundbeck Foundation R266-2017-4331

Title: Striatal dopaminergic signatures of reward-directed behavioral strategies in the rodent Continous Performance Task

Authors: *S. OVROM, S. H. JØRGENSEN, L. P. POSSELT, J. COLL MARQUÈS, M. E.-S. HERVIG, U. GETHER;
Univ. of Copenhagen, Copenhagen, Denmark

Abstract: A crucial responsibility of our brain is to guide attention and select for relevant, goal-related information. Dopamine has long been understood to play a role in this process through its influence on motivation. The densest dopaminergic projections, the mesolimbic and nigrostriatal pathways, project to the ventral striatum (VS) and dorsal striatum (DS), respectively. The striatum is thus the major dopaminergic input center of the brain. Dopamine in the VS is understood to influence behavior by encoding salience of objects and events. The dorsolateral striatum (DLS) is thought to have a closer role in the formation of habits, while the dorsomedial striatum (DMS) plays a role more with the association of action, stimuli, and rewards. Here, we train male C57BL/6 mice to perform the rodent continuous performance task (rCPT), a reward-based attentional task. Using multi-region fiber photometry with the dopamine sensor dLight1.3b, we record real-time, sub-second dopamine dynamics in these mice. With probes in the DLS, DMS, and VS, we are able to identify unique characteristics of each of these striatal subregions which correspond to various events in this task. By manipulating the rCPT task in various ways, we then show that the dopamine dynamics of each subregion respond differentially to these new task parameters. These differences allude to the distinct roles of the subregions. Further, we assess the mice based on several parameters used to describe the behavioral strategy used to complete the rCPT task. We then compare the dopamine responses in each subregion between the two extreme ends of each strategy parameter and use these comparisons to determine which striatal subregions are most closely associated with changes in certain reward-directed strategies. With these results we evaluate the differential roles of dopamine throughout striatal subregions in this learned reward task.

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Poster

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Topic: G.03. Motivation

Title: Semaglutide administration reduces free running as well as motivation for wheel access as measured by progressive ratio in mice

Authors: *E. FOSCUE[1], J. LARA JIMÉNEZ[1], J. R. TRINKO[1], K. STANKEWICH[3], S. L. THOMPSON[1], A. CORSTENS[1], M. SERLIE[2], J. TAYLOR[1], R. J. DILEONE[1];
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Abstract: GLP-1 agonists have recently emerged as powerful treatment options for obesity due to their effects on food intake and body weight. A significant driver of these effects appears to be through their interactions with the motivation and reward systems. While a great deal of research has been conducted into how GLP-1 agonists reduce consumption, relatively few studies have

investigated the effect of GLP-1 agonists on motivated exercise behavior. This gap is particularly relevant because exercise is a behavioral intervention recommended for individuals seeking to lose weight. Here we investigated the effects of repeated semaglutide (SG) administration on exercise in male and female wild-type C57BL/6J mice, in both a free running and a progressive ratio (PR) paradigm. During free running, animals were given unlimited wheel access for two weeks, then injected with 24 nmol/kg/day SG for seven days. During SG administration, along with the expected weight loss, animals reduced their running distance by 37.9% (± 2.7%) compared to baseline, an effect not seen in vehicle-injected or food-restricted controls, suggesting this reduction is occurring independent of body weight loss. Running returned to baseline after cessation of SG injections. Subsequently, mice were trained in modified running wheel cages where wheels were locked, and the animals needed to perform a single noseport entry to earn a ten-minute period of wheel access. They were then trained and tested on a PR schedule to investigate whether SG reduced their motivation for wheel access. Prior to SG administration, mice underwent five days of testing on the PR schedule to establish a baseline response. During the five days of PR testing where they received SG injection, animals were significantly less likely to achieve higher numbers of rewards relative to baseline, as measured by Cox proportional hazards ($p < 0.005$). As with free-running, the mice returned to their baseline levels of responding following the cessation of SG injection. There were no significant sex differences in either the free running or the PR test. These results demonstrate clear effects of SG on total running distance as well as motivation to run, with implications for how SG impacts voluntary exercise.

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Poster

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SERB-CRG/2020/004971

Title: Deep brain stimulation of LH-MFB alleviates stress induced-motivation deficit and upregulates BDNF expression by the epigenetic regulation of the BDNF gene in the hippocampus

Authors: *B. B. DUDHABHATE[1], N. K. SUBHEDAR[2], D. M. KOKARE[3];
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Abstract: Major depressive disorder (MDD) is a complex illness that is frequently associated with a lack of motivation. Abnormal reward processing, changes in neurochemicals, and structural modifications commonly link to depression-induced motivation loss. Deep brain stimulation (DBS) is a highly successful therapeutic method for treating depression that does not respond to other treatments (treatment-resistant depression, or TRD). Researchers have examined multiple brain targets for the treatment of TRD. The lateral hypothalamus-medial forebrain bundle (LH-MFB) is one of these targets. It has been shown to have strong antidepressant effects in both clinical and preclinical depression models. However, a clear consensus on its molecular mechanism remains unexplored. The current project will offer fresh perspectives on the potential for epigenetic modification of the brain-derived neurotrophic factor (BDNF) gene in the hippocampus following DBS of LH-MFB treatment. The rats were exposed to chronic unpredictable mild stress (CUMS) for 42 days, and depressive-like behaviour and reward motivations were assessed. The CUMS rats showed increased immobility time in the forced swim test (FST) and reward motivations in the progressive ratio schedule of reinforcement. However, a decrease in sucrose consumption in the sucrose consumption test (SCT) and body weight were observed. CUMS reduces the BDNF mRNA level and elevates the 5-methylcytosine (5mC) level in the hippocampus. Moreover, CUMS exposure significantly decreased dendritic arborization and length in the neurons of the dentate gyrus (DG). There was a decrease in the levels of dopamine (DA) and serotonin (5-HT) in the hippocampus, along with a reduction in the hippocampal volume. Interestingly, LH-MFB's DBS recovered the rats from anhedonia and behavioral despair while also improving reward motivation. In addition, hippocampal BDNF mRNA, DA, 5-HT levels, and dendritic arbors and length were increased in the CUMS+DBS rats. The elevated level of 5mc was significantly reduced, whereas the hippocampal volume was increased after DBS treatment in CUMS rats. In conclusion, the DBS of LH-MFB regulates the level of 5mc at the IX promotor region of the BDNF gene and influences gene expression, which may suggest a valuable mechanism for the antidepressant effect of the DBS of LH-MFB. The research outcome also increased the validity of LH-MFB as a potential target for DBS in the treatment of depression-like behaviour.

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Poster

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Topic: G.03. Motivation

Support: NIH Intramural Grant Z1ES90998

Title: Acetylcholine Within the Nucleus Accumbens Core Is Elevated During the Acquisition Phase of Wheel Running but Not the Maintenance Phase

Authors: *A. C. LETSINGER[1], J. WU[2,1], D. YOUNGSTROM[3], K. U. TANG[2], J. L. YAKEL[4]; [1]Natl. Inst. for Envrn. Hlth. Sci., Durham, NC; [2]Natl. Inst. of Envrn. Hlth. Sci., Durham, NC; [3]Natl. Inst. of Envrn. Hlth. Sci., Chapel Hill, NC; [4]Neurobio., Natl. Inst. of Envrn. Hlth. Sci., Durham, NC

Abstract: Our objective is to investigate the neurotransmission associated with compulsive-like wheel running behavior in mice with implications for developing interventions to promote human physical activity participation. Dopaminergic activity within the nucleus accumbens is essential for physical activity behaviors, however, modulating dopamine directly can cause many unwanted side-effects. Therefore, we sought to characterize acetylcholine's less-understood local role in wheel running acquisition and maintenance. To measure the relative release of acetylcholine, we utilized single laser fiber photometry with $GRAB_{ACH3.0}$ and TdTomato, to control for movement artifacts, in brain regions associated with emotional valence and motivated behaviors - the ventral hippocampus and nucleus accumbens core (N = 4 males and 4 females). We measured changes in acetylcholine during the acquisition (first 5 days) and maintenance (one month later) phases of wheel running. We employed DeepLabCut to label mouse positions over time and a supervised machine learning program, Simba, to label wheel running with high precision. We then analyzed wheel running bouts compared to 15 seconds pre and post-running using a custom-built R Shiny program, FiPhA. Using these novel methods, we observed that during acquisition and maintenance in the ventral hippocampus, acetylcholine rises 1.15 and 0.73 SDs above baseline as the mouse is running, respectively (P = 0.0032 and P = 0.0287). However, in the nucleus accumbens, acetylcholine is elevated 0.42 SDs above baseline during acquisition and remains unchanged during maintenance (P = 0.0153 and P = 0.9126). These data suggest that acetylcholine plays distinct roles in wheel running behavior in the two regions. As acetylcholine release is intertwined with dopamine release in the striatum, this previously unknown phenomenon may provide insights into the neurotransmission underlying the acquisition of wheel running. Further studies are ongoing to determine whether altering the release of acetylcholine will impact running wheel behavior.

Disclosures: A.C. Letsinger: None. **J. Wu:** None. **D. Youngstrom:** None. **K.U. Tang:** None. **J.L. Yakel:** None.

Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.14/N12

Topic: G.03. Motivation

Title: Activation of cholinergic interneurons in the nucleus accumbens during reward consumption is altered by diabetes

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Abstract: The rising global prevalence of diabetes highlights a critical need to understand the neural mechanisms influencing hedonic eating and food choice in diabetic individuals. Within the brain's reward circuitry, the nucleus accumbens (NAc) is a key region that regulates the anticipatory and consummatory pleasure acquired from food rewards. Cholinergic interneurons in the NAc modulate local release of dopamine in response to palatable food and are particularly sensitive to dynamic fluctuations in insulin. In this study, we aim to investigate how diabetes, a state of chronically altered insulin levels, affects the functional activity of cholinergic interneurons in the NAc to ultimately influence food intake and choice. Adult male ChAT-cre mice (on a C57BL/6J background) underwent stereotaxic intracranial surgeries to receive a Cre-dependent virus expressing the calcium indicator jGCaMP8s followed by implantation of an optical fiber in the NAc. Mice were then treated with either saline (control) or streptozocin (50 mg/kg for 5 consecutive days), a pancreatic beta cell toxin, to induce insulin deficiency and chronic hyperglycemia (n=8 saline, n=9 streptozocin). Using *in vivo* fiber photometry to monitor neuronal activity, we show that cholinergic interneurons in the NAc exhibit increased firing during the approach towards food and a subsequent pause in activity during food consumption. We also provide evidence that diabetic mice show heightened activation of NAc cholinergic neurons during ingestion of high-fat palatable food compared to control mice. Our findings suggest a potential role of striatal cholinergic interneurons in modulating food reward processing in diabetes.

Disclosures: S.O. Brown: None. **R. Durand-De Cuttoli:** None. **J.L. Ables:** None.

Poster

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Program #/Poster #: PSTR358.15/N13

Topic: G.03. Motivation

Support: NSF Grant 2135305

Title: A Role for Dopamine in Modulating Exploratory Activity in Drosophila melanogaster

Authors: *T. SAQUIB[1], G. W. ROMAN[2];
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Abstract: In many animals, novel stimuli elicit behaviors known as specific exploration. Specific exploration is driven by neophilia, which arouses attention by novelty. The central reward system modulates novelty seeking, but the precise neural mechanisms are unknown. In *Drosophila*, dopamine signaling modulates arousal, attention, and learning. Hence, we

hypothesized that dopamine also has an active role in modulating the responsiveness to novelty found in exploratory activity. To understand the molecular mechanisms and neural circuits responsible for neophilia, we used an open-field arena paradigm to measure the locomotor exploration of *Drosophila melanogaster*. We utilized transgenic and pharmacological approaches to examine the role of dopamine in neophilic exploration. The Dop1R1 dopamine receptor plays a crucial role in regulating exploration levels. *Dop1R1*^{f02676} mutants demonstrate increased initial exploratory activity within an open-field arena. Increased exploratory behavior was also observed using pan-neuronal expression of a *Dop1R1* RNAi transgene. Increasing the amount of dopamine in the brain by administrating Levodopa, a precursor to dopamine, and Carbidopa decreased the amount of open-field exploration. Levodopa and Carbidopa's inhibitory effect was absent when applied to the *Dop1R1*^{f02676} mutant fly. These data suggest that dopamine negatively modulates the behavioral responses to novel stimuli.

Disclosures: T. Saquib: None. **G.W. Roman:** None.

Poster

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Topic: G.03. Motivation

Support: NIH Grant DK138131
NIH Grant DK136810

Title: Unlimited Food Availability Induces Overeating and Weight Gain in Mice

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Abstract: Obesity is a major risk factor for multiple chronic illnesses, including diabetes, cardiovascular disease, and psychiatric disorders. While there are many causes of obesity, the primary drivers are changes in the nutritional content of modern diets, and the proliferation of low-cost calorie dense food. While prior studies have demonstrated that increasing the fat content and caloric density of food drives overeating and obesity in mice, fewer studies have tested how increasing the cost of obtaining high-fat food may control overeating and weight gain. Here, we hypothesized that increasing the cost of high-fat food would limit both over-eating and weight gain in mice. To test this hypothesis, we designed a device that dispensed high-fat diet to mice either freely (free access) or after mice completed one nose-poke (nose-poke access), which gave mice access to high-fat diet for sixty seconds. This device fits in the

home-cage with mice and was their only source of food. In both conditions, mice were allowed to access the device around the clock and interact with it as much as they wanted. In our first experiment, we exposed mice (n=6) to alternating five-day phases of free access or nose-poke access for high-fat diet. On average, mice gained 0.64g during the free access phase and lost 0.12g during the nose-poke access phase (two-tailed paired t-test, $p<0.005$), supporting our hypothesis that increasing the cost of high-fat diet, even by as little as one nose-poke, reduced weight gain in mice. In a second experiment, we maintained two new groups of mice on either free-access (n=7) or nose-poke access (n=7) high-fat diet for six weeks. The free-access group consumed 16% more high-fat diet than the nose-poke access group (two-tailed independent t-test, $p=0.038$), and gained 2.7g per week, compared with 1.3g per week in the nose-poke access group (two-tailed independent t-test, $p=0.003$). We conclude that the free availability of calorie dense food promotes overeating, and that imposing a small cost (one nose-poke) reduces high-fat diet intake and weight gain in mice. Our research highlights the importance of environmental modifications as a component of weight management strategies to combat obesity

Disclosures: M.R. Barrett: None. **Y. Pan:** None. **L. Fang:** None. **J. Czarny:** None. **M. Creed:** None. **A.V. Kravitz:** None.

Poster

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Topic: G.03. Motivation

Support: NIDA grant #R15DA051795
Stanley J. Weiss Memorial Fund

Title: Additive summation in Pavlovian conditioning with stimuli predicting the same or different reinforcing outcomes - behavioral mechanisms and neural correlates

Authors: *D. SIEGEL[1], T. BON[2], A. R. DELAMATER[3];
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Abstract: When two separately trained reward-paired cues are presented simultaneously as a compound, food-anticipatory behavior is greater than that observed in the presence of either cue alone (*e.g., Weiss, 1964*). This effect, termed “additive summation,” is crucial for many theoretical models of associative learning (*e.g., Rescorla and Wagner, 1972*). One question asks whether the reward representations that summate during this procedure are selective for reward identities. This idea receives support from experiments showing different levels of food-anticipatory behavior in the presence of compound cues comprised of cues trained with either the same or qualitatively different rewards. However, prior studies differ regarding which of the compounds elicit greater responding *(Watt and Honey, 1997; Rescorla, 1999*). In Experiment 1,

we replicated this procedure. Subjects revealed selective summation, with higher response rates to the “same” vs “different” compound ($p < 0.0001$). However, Watt and Honey (1997) reported greater responding to the “different” compound. These authors used a partial reinforcement procedure that we replicated in Experiment 2. Test results from this study replicated those from Experiment 1, with a higher percent time in the food magazine in response to “same” vs “different” compounds ($p = 0.0147$). In Experiment 3, we explored the neural processes involved in outcome-selective summation. Rats were trained as described for Experiment 1 and were each tested with either “same” compounds, “different” compounds, or cue elements. Various brain regions were immunofluorescence-labeled for activity-dependent proteins phosphorylated during the test session and the dopamine marker tyrosine hydroxylase (TH). We observed marginal decreases in the number of cells activated following the “different” compounds in the retrosplenial cortex ($p = 0.063$) and substantia nigra ($p = 0.077$). This might suggest an interference in reward processing when cues evoke distinct reward representations. We also observed a marginal increase in nucleus accumbens shell cell intensity (a proxy for firing rate, *e.g., Bertran-Gonzalez et al, 2012*; $p = 0.064$), and a reliable increase in cells activated in the ventral tegmental area (VTA), following the “same” compound ($p = 0.027$). When analyzing the proportion of TH+ cells that were activated in the VTA, we also observed a reliable increase in the number of cells activated following both the “same” and “different” compounds ($p = 0.03$). We are in the process of replicating Experiment 3, but these results suggest that outcome-selective summation involves mesolimbic processes.

Disclosures: D. Siegel: None. **T. bon:** None. **A.R. Delamater:** None.

Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

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Topic: G.03. Motivation

Support: NIH Grant DA035432

Title: The effects of chronic stress on future relapse to palatable food seeking after punishment are sex, stressor, and context specific

Authors: *K. BALL;
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Abstract: The long-term success of dietary treatments for overweight/obesity are low because most individuals relapse to unhealthy eating habits within months of starting treatment. Although chronic stress has long been associated with relapse vulnerability in the clinical literature, relatively few pre-clinical studies have used models of relapse that incorporate a chronic stressor. Using classical animal models of relapse that incorporate forced abstinence procedures, we have shown that a history of chronic stress impacts future relapse vulnerability in a sex-dependent

manner. Moreover, SCH-23390, a dopamine D_1-like receptor antagonist, combined with daily stress attenuated chronic stress effects on relapse. In the present study we tested the effect of chronic stress on future context-induced relapse to palatable food seeking after voluntary (punishment-induced) abstinence. Thus, male and female rats were trained to self-administer highly palatable food pellets in Context A and were then exposed to punishment training for 8 days in Context B. During punishment, 50% of food-reinforced lever-presses produced an aversive footshock of increasing intensity (0 - 0.7 mA). Following each punishment session, rats were exposed to one of six treatment conditions: return to home cage (untreated), i.p. saline injection (Stressor 1), 2 hr restraint (Stressor 2), saline injection + restraint, i.p. SCH-23390 (10.0 μg/kg), or SCH-23390 + restraint. Following 6 days of home-cage abstinence, rats were tested for relapse to food seeking in the absence of food or shock in Contexts A and B. Results showed that, for males, a history of either saline injections alone or restraint alone caused an increase in relapse in Context A compared to untreated rats, whereas in females, a history of either stressor alone caused a *decrease* in relapse in Context A. Surprisingly, male rats with a history of combined saline injections + restraint displayed *decreased* relapse in Context A, whereas females receiving both stressors displayed *increased* responding in Context *B*. SCH-23390 prevented or attenuated these effects in both males and females. These results establish that 1) chronic stress has lasting effects on context-induced relapse after punishment-induced abstinence, 2) those effects are dependent on biological sex and context, and 3) they are mediated by activation of dopamine D1-like receptors in both males and females. Finally, these results show that two qualitatively and quantitatively distinct chronic stressors can have the same effect on future relapse-like behavior, whereas in combination, those same stressors can have very different, even opposite, effects on the same behavior.

Disclosures: K. Ball: None.

Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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Topic: G.03. Motivation

Support: R01-NH126178

Title: Striatal serotonin release signals reward value

Authors: *M. G. SPRING[1], K. M. NAUTIYAL[2];
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Abstract: Serotonin modulates diverse phenotypes and functions including depressive, aggressive, impulsive, and feeding behaviors, all of which involve hedonic and motivational circuitry. To date, research has investigated these effects by focusing on dorsal raphe serotonin neurons or single serotonin receptors. While these studies have led to a better understanding of

the heterogeneity of serotonin actions on behavior, they leave open many questions about the timing and location of serotonin influence on neural circuits. Our studies focus on the dorsal striatum (DS) given past work implicating serotonin in the regulation of DS activity and evidence showing serotonin modulates goal-directed behavior. Recent advances in genetically encoded fluorescent biosensors, including the GPCR Activation Based sensor for serotonin (GRAB-5HT), allow the measurement of serotonin release in mice on a timescale compatible with a single reward. Seeking to understand the involvement of serotonin in striatal reward processing, we monitored serotonin levels using GRAB-5-HT in the DS of adult mice during reward-related behaviors ranging from basic reward consumption to learned anticipation. Fluorescent activity was recorded through a fiber optic implanted in the DS at the site of viral expression of GRAB-5HT (AAV9-hSyn-5-HT3.0).
Our results show that DS serotonin signaling encodes reward consumption, external reward value, and internal state in a capacitance based gustometer during the consumption of evaporated milk. Serotonin release reliably preceded the onset of consumption and scaled with reward concentration. Next, we altered the internal state of mice to increase or decrease the subjective value of the reward through either water restriction or devaluation, respectively. In both experiments, there was a tendency for serotonin release to scale with the manipulation's impact on behavior. Finally, the effect of cued anticipation of reward on DS serotonin was measured in an appetitive Pavlovian conditioning paradigm. A reward-related serotonin signal was observed early in training. Following 10 days of paired association, the serotonin signal shifted to begin rising earlier in the trial beginning during the cue that predicted the reward. Additionally, the serotonin signal decreased in magnitude during the reward period by the 10th day of training. Ongoing studies are focused on both characterizing the involvement of DS serotonin in operant behavior and manipulating release (via optogenetics) to determine serotonin's function in reward approach, consumption, and preference.

Disclosures: M.G. Spring: None. **K.M. Nautiyal:** None.

Poster

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NIH Grant R25DA057786-01

Title: Investigating the role of an aPVT-ZI circuit in the explore/exploit tradeoff

Authors: *B. WELLS[1], D. MARCUS[2], M. CRITZ[3], R. OOMMEN[3], G. CHUN[3], M. R. BRUCHAS[4];

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Abstract: The Paraventricular Thalamus (PVT) is a midline thalamic structure that occupies a strategic position as a crucial integrator of interoceptive, affective, and visceromotor input. It in turn projects widely across the forebrain to modulate a variety of motivated behaviors. The PVT is a highly heterogeneous structure, and recent studies examining the behavioral role of the PVT have shown conflicting results, partially driven by a lack of genetic and anatomical specificity within the PVT. The neuromodulatory peptide neurotensin (NTS) is selectively expressed in the anterior PVT (aPVT) and our preliminary data demonstrates that these neurons send excitatory projections to multiple subcortical brain regions, including the Zona Incerta (ZI). Previous studies have shown that the ZI has been implicated in a wide variety of functions including processing sensory information, ingestion, sexual cycles, arousal, attention, and locomotion. The ZI is a heterogeneous, mainly inhibitory nucleus that projects to the periaqueductal gray (PAG) and midbrain dopamine neurons to mediate novelty seeking and reward consumption, respectively. This bidirectional regulation of these behavioral outcomes suggests that the ZI may play a role in toggling between exploration and exploitation in reward seeking. The explore/exploit tradeoff is an evolutionarily conserved computational problem that all mammals face, weighing the costs of exploration of unknown outcomes and resources versus the costs of exploiting a potentially suboptimal outcome of known value. Ultimately, we aim to understand how the aPVT regulates divergent ZI outputs to orchestrate action selection in the explore/exploit tradeoff. To examine this circuit, we injected mice with DIO-GCaMP6s into the aPVT and implanted a fiberoptic into the ZI to record calcium activity during operant reward conditioning. Following FR1 training, we trained the mice in a probabilistic reversal learning assay to model the explore/exploit tradeoff by designating a target port (80% reward probability, 20% non reward) and non-target port (20% non-rew, 80% rew) and reversing these contingencies after 8 target pokes. We find that the aPVT-ZI circuit is broadly inhibited during reward consumption and excited during operant responding for reward delivery. We will further examine the aPVT-ZI circuit through retrograde tracing, electrophysiology, and optogenetics. Understanding how aPVT projections to the ZI influence value-based decision-making can give insight into how dysregulation of action selection in the explore/exploit tradeoff can contribute to neuropsychiatric pathologies.

Disclosures: B. Wells: A. Employment/Salary (full or part-time):; University of Washington. **D. Marcus:** None. **M. Critz:** None. **R. Oommen:** None. **G. Chun:** None. **M.R. Bruchas:** A. Employment/Salary (full or part-time):; University of Washington.

Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.21/N19

Topic: G.03. Motivation

Title: Motivation in teachers to increase physical activation with the implementation of a daily walk: 10,000 steps.

Authors: *E. RAMÍREZ MORENO[1], L. GARCÍA-RÍOS, Jr.[2], J. ARIAS-RICO[3], A. DURAN VALERIO, Jr.[4], C. DIMAS RESENDIZ, Jr.[5], L.-A. RIVERA-RAMIREZ, MD[6], J. HERNÁNDEZ-HERNÁNDEZ, Jr.[7];
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Abstract: Motivation in teachers to increase physical activation with the implementation of a dailywalk: 10,000 steps.**Introduction:** Physical activity is any body movement associated with muscle contractionthat increases energy expenditure above the resting level. The WHO recommends thatadults perform at least 150 minutes of scheduled physical activity per week. Walking is anactivity that doing it in a group generates greater motivation. It is motivation that can predictthe level of physical activity. Mexico is one of the most inactive countries, with higher levelsof amotivation. The objective of this study was to evaluate if there is an association betweenthe coach's motivation for teachers and the increase in daily steps.**Material and methods**: A quasi-experimental, observational, longitudinal intervention wascarried out, lasting 14 weeks in the year 2023, the selection of the sample was non-probabilistic, voluntary, with signed informed consent, respecting the privacy of theparticipants, this project It was evaluated by the ethics committee of ICSa, UAEH. Thestatistical analysis was performed with the STATA version 14 program. The descriptiveanalysis was through means and SD, while the multivariate analysis was performed with TStudent for paired samples. Statistical significance was considered at $p<0.05$ with 95%confidence intervals.**Results and Discussion:** 40 records were obtained, in two calls carried out, of which dueto inclusion criteria, 12% were excluded because they already carried out physical activityaccording to what the WHO stipulates. Only 60% of registered subjects concluded theintervention, 65% being female and 35% male. During the 14 weeks of intervention, a digitalmotivation coach was provided through images, with different ideas on how to increasewalking. daily, 60% of the participants who completed reached between 7,000 to 10,000steps per day, of which 58% were those who remained motivated, sending reports weeklyand mostly those who hoped to lose weight. 28% of participants were eliminated due to lackof commitment and not completing the corresponding evaluations.Changing a person's habits is a very complex task, there are various theories, andbehavioral therapies that can help modify the change in habits. Like this study, the use ofstrategies that include coaching increases success in physical activity interventions.

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Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.22/N20

Topic: G.03. Motivation

Title: Sex differences in striatal dopamine release during voluntary physical activity

Authors: *M. K. TANNER[1], A. A. HOHORST[2], E. B. OLESON[1], B. N. GREENWOOD[3]; [1]Psychology, [2]Integrative Biol., Univ. of Colorado Denver, Denver, CO; [3]Psychology, Univ. of Colorado Denver, DENVER, CO

Abstract: Rodent voluntary wheel running (VWR) is sex divergent; whereby female rats escalate running behavior faster than males. VWR is used to identify factors underlying exercise motivation, but the mechanisms underlying sex differences in VWR remain unknown. Understanding sex differences in VWR escalation could reveal novel strategies to promote physical activity in humans. One theory underlying VWR escalation is that VWR, like human exercise, begins as a goal-directed behavior that becomes habitual. Importantly, the transition from goal-directed to habitual behavior is accelerated in females compared to males, similar to the accelerated VWR escalation observed in female rats. It is well known that dopamine (DA) release in the dorsomedial striatum (DMS) supports goal-directed behavior, while DA release in the dorsolateral striatum (DLS) supports habit. Whether DA is released in these striatal regions during the escalation and maintenance of VWR is unknown, as is whether sex differences exist. Here, we used fast scan cyclic voltammetry to measure DA release in the DMS and DLS during VWR. After guide cannulae implantation into the DMS or DLS, adult, male and female Long-Evans rats were given voluntary access to a running wheel. After 6 and 28 days of VWR, a carbon fiber microelectrode was lowered into the DMS or DLS and DA release during running and non-running epochs were recorded. DA release shifts from the DMS to the DLS in both sexes as VWR escalates, but DLS DA release was greater in females compared to males as escalation begins. These results are consistent with the notion that VWR begins as a goal-directed behavior that becomes a habit and suggests that DLS DA drives the rapid escalation of VWR in females. This study has important implications for the use of VWR as a translational model of exercise motivation.

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Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

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Topic: G.03. Motivation

Support: UNAM-DGAPA- IN300321
CONAHCYT-CBF2023-2024-180
CONAHCYT-CVU 1312468

Title: Discrimination of Electrical Brain Stimulation

Authors: *B. PACHECO GÓMEZ[1], D. VELAZQUEZ-MARTINEZ[2], A. TOSCANO ZAPIEN[3], D. VELAZQUEZ-LOPEZ[4], W. ZEPEDA-RUIZ[5];
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Abstract: Previous studies using rewarding electrical brain stimulation (EBS) as a discriminative cue focused on the discrimination between pulse amplitudes or pulse frequencies. However, discrimination of rewarding stimuli might be affected by the addition of negative valence stimuli such as electric shocks. To determine how the subjects integrate negative stimuli in the discrimination of rewarding EBS, eight Long Evans rats had an electrode aimed at the medial forebrain bundle (MFB) at the hypothalamus level and were trained to hold-down a lever for increasing time intervals (response cost) to obtain reinforcing EBS. Thereafter, rats were trained on a discrimination task where the previously used reinforcing EBS signaled a lever where a response was followed by reinforcing EBS; on randomly alternating trials a -0.6 log EBS signaled an alternate lever where a similar response led to a reinforcer. After mastering discrimination, generalization tests were carried out varying pulse amplitude and response cost. Thereafter, rats were divided in two groups where they could receive an electric shock that accompanied the response or the reinforcer during amplitude generalization tests. Rats learned the discrimination attaining discrimination indexes (DIs) of 90-98%. After variations in the amplitude parameter, orderly generalization gradients were observed and responding to the high-EBS was a function of the amplitude. Addition of an electrical shock to the response or the reinforcer produced steeper generalization functions. These results indicate that rats are able to integrate value of positive and negative aspects of the responses and reinforcer.

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Poster

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Topic: G.03. Motivation

Support: NIH SP0071887

Title: Influence of appetitive stimuli in anxiogenic zones of the Open Field and Elevated Plus Maze tests

Authors: *D. ZAIDI, S. NASKAR, S. G. QUADIR, S. PATEL;
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Abstract: An organism's survival is dependent on continuous risk assessment that involves its ability to balance exploration with avoidance of potential threats in novel environments. For example, mice innately avoid brightly lit and exposed areas to reduce vulnerability to predation and thus increase chances of survival. Behavioral paradigms like the Open Field (OF) and Elevated Plus Maze (EPM) take advantage of this in order to assess anxiety-like and innate avoidance behaviors in rodents. In the OF, the center of the arena is highly exposed, which evokes its innate avoidance of open spaces. Similarly, the open arms of the EPM are devoid of protective barriers, increasing perceived threat and vulnerability, thereby influencing its willingness to explore these areas. This study probes how potential appetitive stimuli can modulate rodent behaviors in traditionally anxiogenic zones by introducing high value food pellets, neutral bedding, or soiled bedding from the opposite sex into the anxiogenic region of the EPM or OF and examining resulting changes in bouts of exploration and time spent in these areas. Introduction of chocolate pellets along different locations of the open arms of the EPM did not significantly alter the time mice spent in open arms. Interestingly, the introduction of opposite sex bedding resulted in a marked increase in open arm time and center time in the EPM and OF, respectively, suggesting a significant revaluation of this anxiogenic zone when exposed to an appetitive social cue. This effect was pronounced in both male and female mice, with males showing a particularly strong response to female bedding, evidenced by significantly increased time spent in the open arms or center zone compared to controls. Furthermore, single-housed animals also showed a robust change in time spent in both anxiogenic zones of the apparatuses. These effects were independent of context and appetitive-cue novelty, as re-exposure to the EPM or OF twice did not increase open arm or center time. The differential impact of these stimuli on behavior underscores the complex nature of how environmental cues are integrated to modify perceived safety and threat. Future studies will investigate the behavioral outcomes related to exposure to opposite sex bedding using quantification of several exploratory and non-exploratory behaviors. Furthermore, we will explore the role of endocannabinoids in modulating exploratory and non-exploratory behaviors within these behavioral tests.

Disclosures: D. Zaidi: None. **S. Naskar:** None. **S.G. Quadir:** None. **S. Patel:** None.

Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.25/N22

Topic: G.03. Motivation

Title: A comparison of two motivational tasks in male and female rats under acute stress

Authors: *S. MUSCOTT, S. KUHN, L. MATUSZEWICH;
Psychology, Northern Illinois Univ., Dekalb, IL

Abstract: Motivation is a complex concept that contributes to or is imbedded within many different behaviors. Motivation for food is important to understand, given the number of health concerns that diet impacts, such as diabetes and cardiovascular disease (Erlanson-Albertsson, 2005). Prior studies have suggested that stress can affect food motivation and reward sensitivity (Warne, 2009), demonstrating increases and decreases in motivation for a palatable reward, depending upon the type of stressor and motivational state. For instance, yohimbine is an alpha-2 adrenoceptor antagonist that induces an acute stress response through the neurotransmitter norepinephrine (Bremner et al., 1996). Stress research has largely examined these behaviors in a highly controlled environmental setting such as an operant box, with a few animal studies examining motivation by assessing ethological behaviors. Therefore, the current research assessed the impact of acute stress on food motivation in male and female rats in the traditional operant box and the naturalistic string pulling task. It is valuable to consider different approaches to assess motivation, especially when considering sex differences in the expression of motivated behaviors, which has been previously shown (Becker, 2009). Male and female rats were tested on a progressive ratio (PR) schedule in an operant box and a similar PR schedule in a string pulling apparatus under control and acute stress conditions. After appropriate training, rats received 0 or 2 mg/kg dose of yohimbine, counterbalanced and were tested in the operant box or string pulling apparatus. Preliminary results during PR suggest an effect of yohimbine in PR Value ($p= 0.004$) and correct lever presses ($p=0.003$), where rats injected with yohimbine pressed the lever more than rats injected with saline and had higher PR values compared; however, no sex differences were observed ($p=0.634$). There was a significant difference between male and female rats in string pulling in string length pulled ($p=0.001$), with females pulling in more string than males; however, no effect of drug ($p=0.975$). Overall, these results suggest that the approach of assessing motivation may be critical to understanding the effects of acute stress for both male and female rats. In considering differences in behaviors between male and female rodents, it may be important to adapt the parameters of behavioral tests to each sex to fully understand the impact of acute stress on motivation for food rewards.

Disclosures: S. Muscott: None. **S. Kuhn:** None. **L. Matuszewich:** None.

Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.26/N23

Topic: G.03. Motivation

Support: NIH Grant MH063649
NIH Grant DA015188

Title: Central amygdala global and D1 neuron activation generates appetitive 'wanting' for sugar, quinine, and electric shock

Authors: *D. NGUYEN[1], K. C. BERRIDGE[2];
[1]Psychology, Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [2]Psychology, Univ. of Mchigan, Ann Arbor, MI

Abstract: Brain mechanisms can create maladaptive desires that are not justified by their outcome value, such as addictions. A laboratory prototype of maladaptive ‘desire unjustified by outcome’ is ‘wanting what hurts’. This has been produced in rats as maladaptive attraction to a noxious ‘shock rod’, caused by pairing optogenetic channelrhodopsin (ChR2) stimulations of central nucleus of amygdala (CeA) neurons with voluntary encounters of the shock-delivering ‘shock rod’. Here we assessed relative contributions of CeA neurons expressing either D1 dopamine receptors, D2 dopamine receptors, or CRF neurotransmitter to mechanisms of shock rod attraction. We report that selective stimulation of D1-expressing CeA neurons is sufficient to induce maladaptive shock rod attraction similar to hSyn-targeted stimulation of all types of CeA neurons, resulting in repeated self-administered shocks. CeA D1 rats and CeA hSyn rats were also sufficiently motivated to overcome a barrier to reach the shock rod, and to seek out Pavlovian cues associated with the shock rod. The results of this experiment reveal a special role for D1-expressing CeA neurons in recruiting mesocorticolimbic incentive motivation circuitry to generate maladaptive ‘wanting what hurts’. In another set of experiments, CeA hSyn and D1 ChR2 stimulation was sufficient to induce eating of chocolate, standard laboratory chow, and even bitter quinine, suggesting a role for CeA global and D1 neuron activation in appetitive feeding processes.

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

Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.27/N24

Topic: G.03. Motivation

Title: Deconstructing the loop: Cortical and subcortical drivers of human hippocampal signaling

Authors: *B. ELLIOTT[1], V. P. MURTY[2];
[2]Psychology, [1]Temple Univ., Philadelphia, PA

Abstract: Novelty is an important learning signal that invigorates goal-oriented behavior via afferent hippocampal (HPC) and cortical (dlPFC) regulation of ventral tegmental area (VTA) dopamine neurons. Structurally, an afferent circuit with the HPC is crucial for regulating sustained signaling of VTA dopamine neurons, while dlPFC drives transient goal-directed signaling. The upward arc of this circuit consists of dopaminergic VTA projections back to the HPC that modulate its physiology, further aiding novelty detection and goal-directed behavior.

However, the extent of these interactions during human behavior remains unclear. We employed a novel analysis of fMRI data from human subjects (n=77) performing a target-detection task intermixed with familiar and novel pictures. Hierarchical linear regressions examined goal-relevant HPC activation and its regulation by the VTA and dlPFC. HPC activation to novel events dynamically predicted subsequent goal-relevant activation in the HPC (β= 0.058, p<0.01). Additionally, dlPFC activation during target trials dynamically predicted goal-relevant activation in the HPC (β= 0.076, p<0.01). Furthermore, both responses were mediated by VTA signaling during target trials. These findings support models of goal-oriented behavior in which HPC regulatory systems in response to novelty and goal-directed dlPFC systems invigorate VTA responsivity which, in turn, modulate goal-directed HPC signaling.

Disclosures: B. Elliott: None. **V.P. Murty:** None.

Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.29/N25

Topic: G.03. Motivation

Support: UNAM-DGAPA-PAPIIT-IN300321
CONAHCYT-CBF2023-2024-180
CONAHCYT-CVU 1312468

Title: Integration of positive and negative aspects or responses and reinforcers

Authors: *D. VELAZQUEZ-MARTINEZ[1], A. TOSCANO ZAPIEN[2], B. L. PACHECO GÓMEZ[3], W. ZEPEDA-RUIZ[4], D. VELAZQUEZ-LOPEZ[5];
[1]Univ. Nacional Autonoma De Mexico., Mexico, D.F., Mexico; [2]Univ. Nacional Autonoma de Mexico, Mexico, D.F., Mexico; [3]UNAM, Mexico City, Mexico; [4]Univ. Nacional Autonoma De Mexico, Mexico, Mexico; [5]Univ. Nacional Autónoma De México., Mexico City DF, Mexico

Abstract: To obtain a reinforcer subjects face response inconveniences (costs, delays, etc.). Also, although reinforcers are satisfying, they also may have inconveniences. To determine how the subjects integrate positive and negative aspects of responses and reinforcers to determine their pursue of reinforcers we used reinforcing electrical brain stimulation (EBS) of the medial forebrain bundle (MFB) at the hypothalamus level. Rats had to respond holding the lever for increasing time intervals (response cost) to obtain a EBS that varied in amplitude in a systematic way across trials (where they could obtain a maximum number of 10 reinforcers). In addition, rats may receive an electric shock that accompanied their first response of the trial or (in a different group of subjects)) that may coincide with reinforcer delivery. Time allocation decreasing hyperbolic function of response requirement. Parallel curves were observed when rats received decreasing amplitudes of EBS. Adding a shock coincident with the response produce a systematic decrease in in time allocation as a function of reinforcer amplitude. However, adding

a shock coincident with reinforcer produced a stepper decrease in time allocation. Pimozide produced differential effects depending on the coincidence of the shock with the response or with the reinforcer. Although rats are able to integrate value of positive and negative aspects or response and reinforcer several possibilities are worth of further exploration: are there different integrators for response cost and reinforcer value or temporal gradients may explain the different integrations?

Disclosures: D. Velazquez-Martinez: None. **A. Toscano Zapien:** None. **B.L. Pacheco Gómez:** None. **W. Zepeda-Ruiz:** None. **D. Velazquez-Lopez:** None.

Poster

PSTR358: Motivated Behavior: Pharmacology and Circuits

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR358.30/N26

Topic: G.03. Motivation

Title: Role of mu-opioid receptors in mediating intra-accumbens melanin-concentrating hormone effects on incentive motivation for palatable food in rats.

Authors: *C. SARDINA[1], M. J. WILL[2];
[1]Univ. of Missouri, Columbia, Lake Saint Louis, MO; [2]Univ. of Missouri, Columbia, Columbia, MO

Abstract: Melanin-concentrating hormone (MCH) projections from lateral hypothalamus to nucleus accumbens (Acb) have been shown to mediate feeding behavior, yet this has not been well characterized in terms of homeostatic vs. hedonic feeding processes. Hedonic feeding is driven by palatability, rather than homeostatic energy deficit, and can be modeled through intra-Acb administration of the selective μ-opioid receptor agonist Acb D-Ala2, NMe-Phe4, Glyol5-enkephalin (DAMGO), which enhances motivation for palatable preferred diets. MCHR1 receptors are widely distributed in the brain, yet the highest expression levels occur in the Acb, well known for mediating reward-motivated behaviors, such as drug use and food consumption. Our lab recently demonstrated that intra-Acb MCHR1 antagonism blocked the increased breakpoint produced by intra-Acb DAMGO in female rats, suggesting a specific role of MCH in mediating the hedonically-driven motivation for palatable food in females. Increasing MCH1R activity within Acb has been shown to promote general feeding in males but not in intact females. However, the effects of MCHR1 activation on incentive motivation for palatable food has not been explored in females. Here, we investigated the effects of an intra-Acb MCH on DAMGO-induced operant responding for sucrose reward during a progressive ratio schedule. After bilateral intra-Acb cannulae surgery and a 7-day recovery period, rats were trained on a fixed ratio to respond to a lever for a sucrose pellet in operant test chambers. Next, all rats were trained and tested under a progressive ratio operant task following concurrent intra-Acb administration of naltrexone (0μg and 20μg/.5μl/side) immediately prior to intra-Acb administration of MCH (0μg, 0.05μg and 0.25μg/.5μl/side) in a counterbalanced fashion. As

expected, DAMGO significantly increased breakpoint and active lever presses, compared to saline, with naltrexone having a sex-dependent influence on this increase. The results of the study demonstrate that MCHR1 within the Acb may be a critical mediator of of hedonically-driven motivation for palatable food.

Disclosures: C. Sardina: None. **M.J. Will:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.01/N27

Topic: G.03. Motivation

Title: How brain signatures, using electro-encephalography (EEG), reveal the temporal process of humor and "a-ha moments" as viewers "get it" during video advertisements.

Authors: *E. SAAD[1], J. G. MARTÍNEZ-GALINDO[2], E. TEMPLE[3];
[1]NielsenIQ Bases, Middletown, NY; [2]NielsenIQ, Bases, Mexico City, Mexico; [3]NielsenIQ, Bases, Cincinnati, OH

Abstract: Moments of insight and humor are characterized by THE moment when you "get it". Research and theory of these moments has suggested this process may include two phases. The 1st phase is hypothesized to be a detection or cognitive phase when an anomaly is detected. Effort is expended as one tries to understand. The 2nd phase is hypothesized to be affective. The processing becomes easier and associated with a positive emotional response as the previously anomalous information becomes fluent. These moments of insight are often used in advertising and are thought by marketers to be helpful in making advertising more enjoyable. We used EEG and eye tracking of video advertising to explore the two-stage theory of humor / "a-ha" moment processing. 40 participants (50% women) aged 21-54 with a census mix of ethnicities watched a video advertisement 3 times for an automotive brand that had a "twist" in the story telling. Continuous EEG coupled with eye tracking was measured. Three frequency-based measures were extracted from the EEG signal and combined across all 3 views: fronto-central alpha/beta asymmetry (indexing emotional approach motivation), fronto-central alpha/theta power (indexing attention), and fronto-central theta/gamma power (indexing memory processing). Our hypothesis was that in the moments before the twist was understood, the EEG pattern would be characterized by high attention index and low in emotional approach. If participants experienced an "a-ha moment", this pattern would flip with high index of emotional approach and lower attention. We observed the hypothesized pattern of response in women from seconds 14-18 in the advertisement when the twist of the advertisement becomes clear. Eye tracking heatmap indicated the viewers were visually focused on the relevant aspects of the stimulus during this time, suggesting the pattern observed was consistent with these aspects of the storyline. Men showed a different pattern, with no cognitive phase. Instead, they showed strong emotional approach throughout the anomalous moment. Their response seemed to be more related to the

heart-warming father / daughter interaction. These results confirm the hypothesized humor signature in a marketing asset and support the approach in advertising when appropriate.

Disclosures: E. Saad: A. Employment/Salary (full or part-time):; NIQ. **J.G. Martínez-Galindo:** A. Employment/Salary (full or part-time):; NIQ. **E. temple:** A. Employment/Salary (full or part-time):; NIQ.

Poster

PSTR359: Motivation: Social Communication and Behavior I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.02/Web Only

Topic: G.03. Motivation

Support: Russian Science Foundation Grant #22-11-00213, https://rscf.ru/en/project/22-11-00213/.

Title: Semantic map of intentionality expressed in natural language

Authors: *A. V. SAMSONOVICH[1,2], A. A. DOLGIKH[1], D. L. KHABAROV[1], G. A. ASCOLI[2];
[1]Natl. Res. Nuclear Univ. MEPhI, Moscow, Russian Federation; [2]George Mason Univ., Fairfax, VA

Abstract: The goal of this study is to build and analyze a semantic map of intentionality expressed verbally during social communications. The notion of intentionality comprises and extends the notions of emotion, affect, mood, intention, and motivation, among others (P. Jacob, Stanford Encyclopedia of Philosophy, 2023). Examples of intentionality would be “express moral support”, “call for frankness”, or “go formal”. The map is built using the Generative Pre-trained Transformer GPT-4 large language model accessible via ChatGPT. Statistical and machine learning analyses reveal the topological and geometric properties for the obtained space of intentionality. Results show that the space of intentionality is far richer than the space of emotions. At the same time, its elements are sufficiently abstract to be applicable to virtually any domain, because they do not include specific objectives such as “place an order”. Furthermore, we found that most intentionalities are highly correlated with each other, and therefore their semantic map forms a relatively low dimensional subspace in the original space of all possible intentionalities. The study connects to the eBICA cognitive architecture framework (A.V. Samsonovich, Cognitive Systems Research, 2020) that operates in terms of appraisals and moral schemas. Selection of relevant intentionalities for eBICA is paradigm-dependent and can be determined empirically in each particular case. The illustrative example used in this work is the paradigm of a cocktail party conversation, supposedly happening at a conference banquet. Results of the experimental study confirm the usefulness of the developed concept.

Disclosures: A.V. Samsonovich: None. **A.A. Dolgikh:** None. **D.L. Khabarov:** None. **G.A. Ascoli:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.03/N28

Topic: G.03. Motivation

Support: NSFC Grant 82371215
NSFC Grant 82171199

Title: Role of serotonergic nerve projection from dorsal raphe nucleus to basolateral amygdala in depressive behaviors

Authors: Y. YOU, ***C. GAO**;
Xuzhou Med. Univ., Xuzhou, China

Abstract: Role of serotonergic nerve projection from dorsal raphe nucleus to basolateral amygdala in depressive behaviorsAuthors Y. YOU, N. SUN, Y.T. SONG, C.T. LV, *C. GAO;Xuzhou Med Univ, Xuzhou, China**Disclosures Y. You:** None. **N. Sun:** None. **Y.T. Song:** None. **C.T. Lv:** None.**C.Gao:** None. **Abstract:** Depression is a mood disorder with significant and persistent downturn as the main clinical feature. Many studies have shown that serotonin (5-HT) neurons in the dorsal raphe nucleus (DRN) are closely related to the occurrence and development of depression, which have neural projections to the basolateral amygdala (BLA), one of the important hubs for regulating emotions. However, the role of serotonergic nerve projection from DRN to BLA ($DRN^{5\text{-}HT}$→BLA) in depressive behaviors is unclear. By chemogenetic technique under the chronic social defeat stress (CSDS) model, we found that the $DRN^{5\text{-}HT}$→BLA neural projection is involved in regulating the depressive behaviors. Activating this neural projection can reverse the depressive phenotype in depression-susceptible (SUS) mice, and inhibiting this neural projection can induce the depressive phenotype in depression-resistant (RES) mice. Based on this phenomenon, we then explored the cellular mechanism. In combination with immunofluorescent and electrophysiological techniques, we found that in depressed state, the activity of 5-HT neurons in DRN decreased, the activity of glutamate neurons in BLA increased, and the activity of GABA neurons decreased, leading to excitation-inhibition imbalance of neurons in BLA, which is the cellular mechanism of $DRN^{5\text{-}HT}$→BLA neural projection involved in regulating depressive behaviors. Furthermore we investigated the synaptic mechanism by western blotting and in vivo microdialysis. We found that in depressed state, the 5-HT neurotransmitter from DRN to BLA is decreased, meanwhile, the expression of $5\text{-}HT_{1A}R$ in glutamate neurons and $5\text{-}HT_{2A}R$ in GABAergic neurons in BLA is decreased, which lead to the increased activity of glutamate neurons and the decreased activity of GABAergic neurons in BLA. It is the synaptic mechanism of $DRN^{5\text{-}HT}$→BLA neural projection involved in regulating depressive behaviors. Overall, we discovered a new neural projection involved in the regulation of depressive behaviors——the $DRN^{5\text{-}HT}$→BLA neural projection, and elucidated its cellular and synaptic mechanisms involved in the regulation of depressive behaviors, providing

new insights and targets for the research on the occurrence and development mechanism of depression and related treatment strategies.

Disclosures: Y. You: None. **C. Gao:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.04/N29

Topic: G.03. Motivation

Title: Pharmacological manipulation of distress modulates helping behavior in a rodent model of altruism

Authors: E. KETTERER-SYKES[1], E. SARACENO[1], F. HOUGH[2], M. WYSE[1], G. RESTIFO-BERNSTEIN[2], A. BLAIS[1], M. KHONDOKAR[1], P. HOEN[1], ***H. H. LOPEZ**[2];
[1]Neurosci., [2]Psychology, Skidmore Col., Saratoga Spgs, NY

Abstract: Exploring the psychobiological antecedents of altruism may help us unravel psychopathological dysfunction in human empathy, as well as develop ways to promote altruistic behavior in society. Neurobehavioral experimentation on altruism has benefitted greatly from the trapped rat model. Free rats are willing to liberate a trapped cagemate, and such behavior is influenced by a variety of developmental, environmental, and social factors. Emotional contagion theory argues that an organism's distress can "spread" to a potential helper; the helper is then motivated to engage in altruism, in part to alleviate their own negative emotions. The present study investigated whether pharmacological manipulation of distress can affect emotional contagion and altruistic motivation. 120 Sprague-Dawley rats (30 male pairs and 30 female pairs) completed 12 daily trials in the trapped rat procedure. During an individual trial, the designated trapped rat was placed in a restrainer in the center of an open field, while its cagemate could move around freely and possibly open the restrainer by lifting a door. Trapped rats received an intraperitoneal injection of either 1) physiological saline, 2) the anxiolytic midazolam (1.5 mg/kg), or 3) the anxiogenic yohimbine (2.5 mg/kg) 30 minutes prior to the start of each trial. Dependent variables measured were: 1) door opening latency (sec), 2) percentage of trials in which a door opening occurred, and 3) the number of free rats classified as "openers." We predicted that free rats paired with midazolam-subjects would show attenuated altruistic behavior (e.g., higher door opening latency) compared to controls, and that, conversely, free rats paired with yohimbine-subjects would show enhanced altruistic behavior. Several interesting results were observed. First, there was a significant sex-difference, in that more females (across all drug conditions) were classified as openers than males. This supports previous evidence that females express higher altruistic motivation than males. Second, midazolam-treatment significantly attenuated altruistic behavior. From trials 4-12, free rats paired with midazolam-subjects expressed slower door opening latencies compared to controls. Third, yohimbine-treatment significantly increased altruistic behavior (e.g., reduced door opening latencies) - but

only on trials 1-3; by trials 9-12, this pattern was reversed. These results are consistent with emotional contagion theory and indicate that intensity of distress affects altruistic motivation.

Disclosures: E. Ketterer-Sykes: None. **E. Saraceno:** None. **F. Hough:** None. **M. Wyse:** None. **G. Restifo-Bernstein:** None. **A. Blais:** None. **M. Khondokar:** None. **P. Hoen:** None. **H.H. Lopez:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.05/N30

Topic: G.03. Motivation

Support: NIH Grant R01 MH125408

Title: Characterization of oxytocin receptor-expressing medium spiny neurons projections in the socially monogamous prairie vole

Authors: *F. DUCLOT[1], L. J. YOUNG[2], Z.-X. WANG[3], M. KABBAJ[1];
[1]Biomed. Sci., Florida State Univ., Tallahassee, FL; [2]Ctr. for Translational Social Neurosci., Emory Univ., Decatur, GA; [3]Psychology & Neurosci., Florida State Univ., Tallahassee, FL

Abstract: Social affiliation is a core characteristic of human social behaviors and its impairments are a common feature related to several neuropsychiatric illnesses including schizophrenia and autism spectrum disorders. Thereafter, understanding the neurobiology of social attachment is of critical importance. In this context, the socially monogamous prairie vole (*Microtus ochrogaster*) has revealed that the neurobiology of pair bonding involves a variety of neurotransmitters and brain areas with, for instance, a critical role played by oxytocin and its receptor (OTR) in the nucleus accumbens (NAc). Notably, the NAc contains distinct subpopulations of medium spiny neurons (MSN) with projections to the ventral pallidum (VP) and/or the ventral tegmental area (VTA), known to differentially modulate motivated behaviors. The projection pattern of MSN differs between species as most VTA-projecting MSN also send collaterals to the VP in mice but not in rats. Unlike in mice and rats, OTR is expressed post-synaptically in prairie voles, which highlights the need to identify the downstream target(s) or OTR-expressing MSN in this socially monogamous species. In this study, we thus aimed at characterizing the projections of OTR-expressing MSN to the VP and VTA using a combination of virally-mediated tracing approaches. First, the overlap in VP- and VTA-projecting neurons was examined in the general MSN population by injecting adult sexually naïve prairie voles with retrograde adeno-associated viruses (retroAAV) constitutively expressing enhanced green fluorescent protein (EGFP) or mCherry in the VTA or the VP, respectively. Following two weeks of recovery and viral expression, we found very few cells double-labeled for EGFP + mCherry in the NAc, indicating that in prairie voles, few MSN projecting to the VTA also send collaterals to the VP. Second, we examined the extent of such collaterals specifically in OTR-

expressing MSN by injecting retroAAV expressing EGFP in a Cre-dependent manner in the VTA alongside retroAAV constitutively expressing mCherry in the VP (and vice-versa) in transgenic prairie voles expressing the Cre recombinase under the OTR gene promoter. Three weeks later, no overlap in EGFP and mCherry signal was observed in the NAc, indicating that while OTR-expressing MSN do project to the VTA or the VP, they do not appear to send collaterals to these target areas, in line with the general MSN population. Altogether, our observations indicate that in prairie voles, the populations of accumbal MSN projecting to the VP and the VTA are mostly distinct, and that the subpopulation of MSN expressing OTR follows the same projection pattern.

Disclosures: F. Duclot: None. **L.J. Young:** None. **Z. Wang:** None. **M. Kabbaj:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.06/N31

Topic: G.03. Motivation

Support: NIH Grant R01GM148960
NIH Grant P20GM125508

Title: Neural activities in social and asocial populations of the free-swimming fish.

Authors: *M. HASEGAWA[1], V. LIMA FERNANDES[3], M. PUGH DE LOS REYES[4], M. IWASHITA[2], M. YOSHIZAWA[2];
[2]Sch. of Life Sci., [1]Univ. of Hawai‘i at Mānoa, Honolulu, HI; [3]Inst. de Biologie Valrose, Univ. Côte d’Azur, Nice, France; [4]Dept. Biol. Sci., USC, Los Angeles, CA

Abstract: Most known cave animals are asocial and have adapted to cave habitats in a relatively short amount of time (thousands to ten thousand years). These asocial species are thought to have impaired social decision-making neural networks due to disuse. Indeed, cavefish show dysregulated gene expression in neural genes, exhibiting a large overlap in the same directional expression changes (over or down regulations) seen in the brains of patients with autism (>58.5% of 3,152 cavefish orthologs). The low-social line of honeybees also showed the similar expression dysregulation. These analyses for differentially expressed genes among honeybees, cavefish, and humans indicated the shared dysregulation of the dopaminergic and GABAergic systems. Despite gene dysregulation and potential neural network impairment, recent studies by our team and our collaborators suggested that sociality is promoted through ketosis (via fasting, ketogenic diet, or ketone body supplementation) in both asocial cavefish and patients with autism. This social retrieve was unexpected, and its neural mechanism has not been well-studied. In this study, we examined the differing neural activities between social and asocial populations, as well as the neural activities induced by ketosis in the Mexican tetra, *Astyanax mexicanus*, which consists of riverine social (surface fish) and cave-dwelling asocial populations (cavefish).

We mapped their active neurons in the cleared brains using the CUBIC protocol. Phosphorylated ERK (pERK) was used as a marker of active neurons. We found that a basolateral amygdala comparable region (Dm in fishes), and olfactory bulbs were strongly pERK positive (active neurons) in any conditions in both social surface and asocial cavefish, suggesting that they could be with emotion (either positive or negative) and received olfactory inputs during a behavioral assay. Habenula were active under a stress-associated new-environmental stimulus but were low in a familiar environment in both surface fish and cavefish, confirming a known response of habenula. We found that the preoptic area (POA) and striatum comparable areas (Vc/Vd) (both are known as a part of the social decision-making network) were strongly activated in surface fish under the social affinity-inducing condition, while the activation of POA and Vc/Vd was weaker in cavefish. One month of the ketogenic diet treatment reduced habenula activities while POA and Vc/Vd activities stayed at similar levels with the control diet. In conclusion, our results indicated that ketosis promoted social affinity by lowering habenula activities.

Disclosures: M. Hasegawa: None. **V. Lima Fernandes:** None. **M. Pugh de los Reyes:** None. **M. Iwashita:** None. **M. Yoshizawa:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.07/N32

Topic: G.03. Motivation

Support: OD011092
AA013510

Title: Assessing the Efficacy of Social Video as a Reinforcement Stimulus in an Open Economy Context in Rhesus Monkeys

Authors: *G. L. RAMIREZ OVALLE[1], A. KISTNER[2], L. R. LURYE[3], R. KHADKA[4], D. ZARAZA[5], K. GRANT[6];
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Abstract: Rationale A vast majority of studies involving non-human primates (NHPs) in behavioral neuroscience protocols use either food or fluid reinforcement. The reliance on ingesta may confound neural circuitry investigations of associative learning towards mechanisms that defend food or fluid homeostasis. However, NHPs are highly visually oriented, offering an opportunity to employ visual displays, particularly species-relevant videos, as an alternative reinforcer. To date the reinforcing efficacy of video clips to maintain operant responding has not

been assessed systematically. **Objectives** To determine the reinforcing efficacy of short videoclips in which monkeys are engaged in social interaction (i.e., social videos), this study uses progressive ratio schedules of responding on computer-controlled touchscreens. **Methods** A group of twelve (equal sex) rhesus macaques were trained on instrumental Fixed Ratio (FR) and exponential progressive ratio schedules resulting in a 10 sec social video display. All monkeys were housed in the same room and all had their operant sessions run simultaneously. Reinforcing efficacy (fit to a demand curve) was assessed with both between sessions increases in response ratio (2 session each FR) and within session increase in response ratio. Increments of response requirement followed this pattern: FR2, 4, 8, 16, 32, 64 and 128. **Results** Contingent display of 10 sec video clips of monkeys engaged in social activities maintained responding up to an average break point of FR 32 (for the between session increase in FR) and FR 128 (for the within session increase in FR). There were no sex difference in breakpoints. **Conclusions** Short video clips of species-specific monkeys (rhesus) can robustly maintain responding and fit the mathematical equation of a demand curve, demonstrating the possibility of an alternative to food or fluid in NHP studies assessing associative learning and performance

Disclosures: G.L. Ramirez Ovalle: None. **A. Kistner:** None. **L.R. Lurye:** None. **R. Khadka:** None. **D. Zaraza:** None. **K. Grant:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

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Topic: G.03. Motivation

Support: R01MH114882
R01MH127820
R01MH104559
R01MH120514
R01MH120637
1K99DA058213-01

Title: A critical role for cortical amygdala circuitry in shaping social encounters

Authors: *A. AUBRY[1], R. DURAND-DE CUTTOLI[1], E. KARPMAN[2], L. F. PARISE[3], K. CHAN[4], H.-Y. LIN[5], J. ALVAREZ[6], S. J. RUSSO[7];
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Abstract: Aggression is an evolutionarily conserved behavior that controls social hierarchies and protects valuable resources like mates, food, and territory. In mice, aggressive behavior can be broken down into an appetitive phase, which involves approach and investigation, and a consummatory phase, which involves biting, kicking, and wrestling. By performing an unsupervised weighted correlation network analysis on whole-brain c-Fos expression, we identified a cluster of brain regions including hypothalamic and amygdalar sub-regions and olfactory cortical regions highly co-activated in male, but not female aggressors (AGG). The posterolateral cortical amygdala (COApl), an extended olfactory structure, was found to be a hub region based on the number and strength of correlations with other regions in the cluster. Our data further show that estrogen receptor 1 (ESR1)-expressing cells in the COApl exhibit increased activity during attack behavior, and during bouts of investigation which precede an attack, in male mice only. Chemogenetic or optogenetic inhibition of COApl ESR1 cells in AGG males reduces aggression and increases pro-social investigation without affecting social reward/reinforcement behavior. We further confirmed that COApl ESR1 projections to the ventrolateral portion of the ventromedial hypothalamus and central amygdala are necessary for these behaviors. Collectively, these data suggest that in aggressive males, COApl ESR1 cells respond specifically to social stimuli, thereby enhancing their salience and promoting attack behavior.

Disclosures: A. Aubry: None. **R. Durand-De Cuttoli:** None. **E. Karpman:** None. **L.F. Parise:** None. **K. Chan:** None. **H. Lin:** None. **J. Alvarez:** None. **S.J. Russo:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

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Program #/Poster #: PSTR359.09/N34

Topic: G.03. Motivation

Support: MH109450
MH058616

Title: Role of ten-eleven translocation 2 (Tet2) in pair bonding in prairie voles

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Abstract: Socially monogamous prairie voles form enduring social attachments, displaying a preference for their partner over a stranger and a selective aggression towards unfamiliar conspecifics. Epigenetic changes such as histone modifications and DNA methylation play an important role in the modulation and maintenance of gene expression and behavior. Here we examined the role of ten-eleven translocation (Tet) enzymes, which are implicated in DNA

demethylation, in pair bonding. We focused on the Nucleus Accumbens (NAc), which has been shown to play an important role in partner preference. Our data show that Tet2 mRNA levels, but not Tet1 or Tet3, are upregulated in the NAc of pair-bonded female prairie voles after 2 weeks of cohabitation with a partner, compared to sexually naïve females. However, there was no increase in Tet2 mRNA levels after 24hrs of cohabitation. These findings suggest that Tet2 may play a role in bond maintenance. We thus hypothesized that knockdown of Tet2 would impair bond maintenance. To test this, an Adeno-Associated Virus expressing either a Tet2-shRNA or a scrambled sequence (scr-shRNA) was injected bilaterally into the NAc of female prairie voles. Three weeks after injections, the females were paired with a partner. After two weeks of cohabitation, they were tested for partner preference. When given a choice between their partner and a stranger during a Partner Preference Test, female prairie voles that were injected with the Tet2-shRNA spent less time in side-to-side contact with their partner compared to controls. To determine if social recognition was impaired by the knockdown of Tet2, sexually naïve females received bilateral injections of either the Tet2-shRNA or scr-shRNA in the NAc and underwent a Peer Preference Test and a Social Discrimination Test. During the Peer Preference Test, subjects were given a choice between their cage mate since weaning or a novel animal. Females injected with the Tet2-shRNA spent less time with their cage mate and more time with the stranger compared to controls. Sexually naïve females injected with the Tet2-shRNA also displayed increased social novelty-seeking behavior compared to controls during the Social Discrimination Test, spending more time interacting with a novel than the familiar animal. An investigation of the gene expression alterations induced by Tet2 knockdown in the NAc is currently under way to examine the molecular underpinnings. Taken together, these observations suggest that Tet2 in the NAc plays an important role in pair bonding maintenance by reducing interest in novel male prairie voles.

Disclosures: M. Crawford: None. **F. Duclot:** None. **L.L. Sailer:** None. **A. Akbarabadi:** None. **I. Rowe:** None. **D. Stewart:** None. **Z. Wang:** None. **M. Kabbaj:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

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Program #/Poster #: PSTR359.10/

Topic: G.03. Motivation

Support: NIH-NINDS 75N95023P00045

Title: Elevating underrepresented voices in STEM: A comprehensive curriculum's impact on student success and preparedness for summer internships

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Abstract: In the pursuit of diversifying the scientific landscape, underrepresented students often encounter obstacles in accessing competitive summer internships due to limited exposure to research during their undergraduate studies. Tailored educational initiatives are imperative to equip these students with the essential skills and knowledge necessary for successful participation in such opportunities.We hypothesize that implementing a neuroscientific focused curriculum within the Scientific Research and Preparatory Program (SRPP) will yield significant enhancements in content knowledge among freshman and sophomore undergraduate students with limited research exposure. The SRPP endeavors to empower underrepresented students within the scientific community through a strategic design tailored to equip them for competitive summer internships in the United States. The curriculum includes components such as Introduction to Research, Biology Exploration with a neuroscience emphasis, Professional Development, College Readiness, and Career Exploration.A rigorous evaluation methodology assessed both professional resources and student progress, revealing significant increases in content knowledge, particularly during Weeks 2 and 4. Despite variations, the majority of students consistently exhibited heightened knowledge, affirming the curriculum's effectiveness in addressing the identified educational gap.In conclusion, the implementation of a neuroscientific focused curriculum within the SRPP has proven highly effective in addressing the educational gap faced by underrepresented students in accessing competitive summer internships. Through this initiative, students demonstrated significant enhancements in various critical aspects, including research principles, biology with a neuroscience focus, and professional skills such as communication and networking. Additionally, the curriculum has prepared students for college and career readiness, empowering them to make informed decisions about their future pathways. These findings underscore the importance and efficacy of tailored educational initiatives in equipping underrepresented students for successful participation in the scientific community.

Disclosures: M.P. Méndez-González: None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.11/N35

Topic: G.03. Motivation

Title: Intranasal Oxytocin and L-Dopa Alter Social Motivation in Mice as Measured by the Weighted Door and Ladder Task

Authors: C. WELLS[1], K. PERSSICO[2], S. BROWN[3], J. KITTRELL[1], A. MARRISON[4], D. CHICK[1], I. JACOBER[5], K. EVANS[6], *T. ROGERS[1];
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Abstract: Social motivation is a driver of social interaction and is reduced in multiple clinical disorders including autism spectrum disorders, depression, and schizophrenia. We recently developed and validated two measures of social motivation for mice: the ladder task and the weighted door task. These tasks require mice to exert increasing effort to access a social partner. The mouse's willingness to exert effort to access a social partner by climbing a ladder that becomes increasingly steep across trials or by pushing a weighted door that becomes increasingly heavy across trials demonstrates their motivation for social interaction. As we have previously measured differences in social motivation between mouse strains, including C57, DBA, and BTBR strains, we currently aim to demonstrate that social motivation can be manipulated by altering CNS oxytocinergic and dopaminergic activity. Male and female, adult C57BL/6J mice were administered oxytocin, L-dopa, or saline intranasally and then tested on the ladder task and weighted door task. In the weighted door task, oxytocin increased the frequency of approaching the weighted door as compared to saline and L-dopa in early trials with less weight. However, in later trials with higher weight, the oxytocin groups approached the door with the least frequency. L-dopa administration was associated with maintaining a high frequency of door approach over the later trials / higher weights. Time spent pushing the door was higher in later trials when mice were administered L-dopa as compared to saline and oxytocin. In the ladder task, oxytocin administration produced the shortest latency to climb the ladder when at the earliest trials in which the ladder is horizontal, but oxytocin administration produced the highest latency in later trials with increased steepness. L-dopa administration resulted in sustained lower latency compared to saline across the trials. Taken together, the intranasal administration of oxytocin is associated with increased social interaction when low effort is required and decreased social interaction when high effort is required suggesting a decrease in social motivation. However, L-dopa is associated with sustained motivation as required effort increases suggesting an increase in social motivation. Understanding the neurochemical basis of social motivation will further the development of pharmacological treatments for decreased social motivation in clinical disorders.

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Poster

PSTR359: Motivation: Social Communication and Behavior I

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Topic: G.03. Motivation

Support: NIH R01MH105592
Lieber Institute for Brain Development Internal Funding

Title: Molecular profiling of the human lateral septum identifies transcriptionally distinct cell subpopulations

Authors: *Y. DU[1], R. A. PHILLIPS, III[1], S. OH[1], S. V. BACH[1], J. E. KLEINMAN[1,2], T. M. HYDE[1,2,3], S. HICKS[5,6,7,8], S. C. PAGE[1,2], K. MARTINOWICH[1,2,4,9];
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Abstract: The lateral septum (LS) is a subcortical structure located along the medial boundary of the lateral ventricles. The LS regulates social behaviors that are frequently impaired in neurodevelopmental disorders including schizophrenia and autism spectrum disorder. Mouse studies identified neuronal subpopulations within the LS that control different facets of social behaviors. Murine LS subpopulations can be distinguished by the presence of different molecular markers, including genes that encode the vasopressin receptor, oxytocin receptor, and corticotropin releasing hormone receptor. However, a comprehensive atlas of molecular profiles for LS cell types in the human brain is lacking. Here we used postmortem human brain tissue samples (n= 3 neurotypical donors) to construct the first transcriptomic profile of human LS. We confirmed the inclusion of the LS on each tissue block by probing for the marker gene *TRPC4* (transient receptor potential cation channel subfamily C member 4) using RNAscope multiplex single-molecule fluorescence *in situ* hybridization. Tissue blocks were scored to isolate the LS, and nuclei were labeled with an anti-NeuN antibody to enrich the samples for neuronal nuclei. We then generated molecular profiles for human LS cell types using single nucleus RNA-sequencing (snRNA-seq) with the 10x Genomics Chromium platform. Following quality control, we retained 9225 nuclei from the LS and surrounding regions. Four transcriptionally distinct neuronal populations within the human LS were identified based on the expression of *TRPC4* and *DGKG* (diacylglycerol kinase gamma). Differential expression analysis identified a population of LS neurons marked by *OPRM1* (opioid receptor mu 1) and further identified a novel, human-specific marker gene, *FREM2* (FRAS1 related extracellular matrix 2) for LS neurons. Some transcriptionally distinct neuronal subtypes originated from different positions along the anterior-posterior axis of the human LS. This data supports the idea that LS cell types are transcriptionally distinct and spatially organized in humans, similar to observations in mice. The current study facilitates our understanding of the cytoarchitecture in the human LS and highlights the need for a spatially resolved transcriptomic profile of the human LS. To further investigate the spatial organization of transcriptionally distinct cell subtypes, future studies will focus on retaining spatial information in the human LS.

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Poster

PSTR359: Motivation: Social Communication and Behavior I

Location: MCP Hall A

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Program #/Poster #: PSTR359.13/N37

Topic: G.03. Motivation

Support: R01MH112504 awarded to JFC and MRR

Title: Examining the role of the endocannabinoid system in reward and aversion in social contexts

Authors: *R. STRICKLAND[1], S. PARDO[1], L. WATSON[2], M. R. ROESCH[3], J. M. WENZEL[1], J. F. CHEER[4];
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Abstract: Social interaction is fundamental to survival. Despite this, the neural mechanisms of social behaviors remain unclear. Previous research has used a Pavlovian social distress procedure to examine social behavior in rodents during rewarding and aversive predictive cues and outcomes. In this procedure subjects are presented with cues predicting the delivery of food, foot shock, or nothing to themselves or their cage-mate located on the other side of a divider. This task has been employed in rats to show that the presence of a conspecific decreases cue-induced responding to threat and motivates empathy-related and consolation-like behavior. The purpose of this study was to determine if these behaviors could be recapitulated in a mouse model, and to examine how systemic endocannabinoid agonist and antagonist administration affects reward and aversion in social contexts. To this end male and female mice were trained on this procedure and then underwent 9 test sessions on which they received various doses of the endocannabinoid antagonist AM251, the agonist JZL187, the agonist URB597, each agonist in conjunction with AM251, or vehicle. Behavior was recorded and scored by blinded observers for each test session. We found that mice exhibited similar behavior as rats, demonstrating conserved empathy-related and consolation-like behaviors. Further, endocannabinoid manipulations significantly altered several behavioral outcomes in males and females, such as approach towards the conspecific during shock delivery or cues that predict shock. These data suggest a role for endocannabinoid signaling in socially-determined behaviors during reward and aversion.

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Poster

PSTR359: Motivation: Social Communication and Behavior I

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Topic: G.03. Motivation

Support: National Institute of Mental Health Grant R01MH119250
C.M. Robertson Foundation

Title: The Dynamics of Basal Amygdala Neuronal Activity in Maternal Behavior

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Abstract: Pup retrieval, a fundamental aspect of maternal care in rodents, relies on sensory cues for successful execution. Previous research has highlighted the crucial role of glutamatergic projections from the basal amygdala to the auditory cortex (BA-AC) in integrating olfactory and auditory cues during this behavior. However, the precise temporal dynamics of BA-AC neurons are still unknown. This study aims to unravel the activity patterns of BA-AC neurons throughout distinct phases of pup retrieval using a novel cued retrieval task in mice. We measured BA-AC neuronal activity using fiber photometry via targeted viral strategies across various behavioral epochs, including approach, contact, retrieval, and pup drop phases. Analysis revealed distinct neural patterns during each behavioral phase, with variability observed between individual mice. Histological examination of fiber placement suggested sub-region specificity within the basal amygdala, contributing to the observed neural patterns. These preliminary findings reveal the complexity of neural dynamics underlying maternal behavior, highlighting the need for a nuanced approach, such as integrating GRIN lens imaging, to decipher the variability observed in neural responses.

Disclosures: H. Ansari: None. **S. Rahman:** None. **S.D. Shea:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

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Topic: G.03. Motivation

Support: DFG, German Research Foundation (Deutsche Forschungsgemeinschaft)

Title: Behavioral Effects of Social Buffering in An Animal Model for Social Anxiety Disorder

Authors: *E. SALUR[1], I. ZOICAS[2], A. SCHMITT-BÖHRER[1];
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Abstract: Humans are inherently driven to connect with others, partly for the stress-reducing benefits. Merely having a companion present can alleviate anxiety, stress, depression, and even physical pain, a phenomenon called “Social Buffering (SB)”. Conversely, social interactions can be perceived as threatening, contributing to Social Anxiety Disorder (SAD), the most prevalent

anxiety disorder, affecting 12-16% of individuals, with more prevalence in women (1.5 to twice as high as in men). Approach-avoidance conflicts in social situations are a hallmark symptom of SAD.
To provide a deeper understanding of the neurobiological mechanisms underlying social fear, basic research is needed. In the quest for an animal model suited to perform this research, the Social Fear Conditioning (SFC) paradigm in rodents emerged as a promising option since it fulfills the criteria for a robust animal model of SAD, demonstrating face, predictive, and construct validity. Through SFC, rodents learn a voluntary social behavior, -approaching an unfamiliar conspecific - results in mild footshocks. Thus, they associate social contact with aversive consequences, generating a conflict between approach and avoidance of social interaction.
SB is recognized for its positive impact in animal model studies but has not been studied in the context of social fear induced by SFC. Our study investigates how social support influences behavior in the face of induced social fear while unfolding sex differences. Within this comprehensive approach, we employ SB in tactile, visual, and olfactory forms both in female and male C57BL/6J mice. Using this paradigm, behavioral effects and underlying neurobiological mechanisms of social fear induction and modulation of this fear through social buffering can be studied. Improved insights particularly in possible sex differences could lead to the development of more therapeutic options and better outcomes for SAD patients.

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Poster

PSTR359: Motivation: Social Communication and Behavior I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.16/N40

Topic: G.03. Motivation

Title: Social isolation effects on hedonic drive and hypothalamic orexin in CD-1 mice

Authors: *R. P. WATERS, **H. MCNERNEY**;
Biol., Univ. of Mary Washington, Fredericksburg, VA

Abstract: Social stress is a primary instigator of mood disorders in humans. While social stress results from social dominance relationships, social isolation is an intense psychosocial stressor for social organisms (including mice and humans) that can have profound effects on physiological and neurobiological systems. One of these negative effects is a loss of feelings of reward, or anhedonia. Feeling ‘good' in response to positive stimuli, or hedonic drive, is largely controlled by hypothalamic orexins. The aim of this work was to investigate the effect of chronic social isolation on hedonic drive and orexin expression in female mice. In addition, this research developed a novel method to assess individual voluntary wheel activity in social cages. After 54 days of treatment, socially isolation (SI) increased hyperactivity and anxiety-like behavior, and reduced hedonic drive. SI also resulted in lower plasma corticosterone levels. Finally, SI resulted

in decreased orexin levels in the hypothalamus. Our results suggest that decreased hedonic behavior induced by social isolation stress is associated with decreased corticosterone and a reduction in orexin, likely in the perifornical area of the lateral hypothalamus of female CD-1 mice.

Disclosures: R.P. Waters: None. **H. McNerney:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.17/O1

Topic: G.03. Motivation

Support: UB PMY IFR

Title: Effects of environmental enrichment on social motivation in young adult female Fischer 344 rats

Authors: *K. ISHIWARI[1], C. R. BRUNO[2], S. HAJ-DAHMANE[1], R.-Y. SHEN[1], D. M. DIETZ[1];
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[2]Neurosci. Program, State Univ. of New York, Univ. at Buffalo, Buffalo, NY

Abstract: Social motivation drives social interactions and is crucial for the development and maintenance of normal social behaviors. Aberrant social motivation may underlie social impairments observed in neuropsychiatric conditions such as autism spectrum disorder, ADHD, schizophrenia, and depression. Environmental enrichment has been shown to produce a variety of beneficial neurobehavioral effects in animal models of a number of neuropsychiatric disorders. The present study examined the effects of environmental enrichment on social motivation in young adult female F344 rats. Starting on about postnatal day 30, female F344 rats were housed either in pairs in standard plastic laboratory cages (N=12) or in a group of 14 in a complex environment consisting of a large multi-level cage filled with pet toys (N=14). After six weeks of differential housing, the two groups were tested in young adulthood on an operant social reinforcement test, which employed an automated three-chamber apparatus with social stimulus chambers on the left and right sides of the central test chamber. During the daily 30-min test session, rats placed in the test chamber were allowed to make snout-poke responses to gain access to a social stimulus (conspecific) placed in one of the side chambers. The sliding doors to the narrow cylindrical ports connecting the test and stimulus chambers opened response-contingently according to a fixed-ratio 5 schedule of reinforcement and allowed the test and stimulus rats to contact snouts and vibrissae. Rats were initially habituated to the test chamber with no social stimulus in either side chamber for seven sessions. A novel social stimulus of the same sex was then introduced into one of side chambers, and rats were tested for responding for the social stimulus for 15 sessions. This was followed by a progressive ratio (PR) test in which

the number of snout pokes required to gain access to the social stimulus was increased progressively. The results demonstrated that the rats reared in a large group in the complex environment made a significantly smaller number of responses for the social stimulus and spent significantly less time contacting the social stimulus than the standard-housed rats, although the enriched rats directed a greater proportion of their responses toward the social stimulus when the social stimulus became more familiar. The PR test showed that the standard-housed rats had a significantly higher break point than the enriched animals. Taken together, our results suggest that being group-housed in complex rearing environments may fulfill animals' needs to interact with conspecifics, thereby reducing affiliative social motivation in healthy animals.

Disclosures: K. Ishiwari: None. **C.R. Bruno:** None. **S. Haj-Dahmane:** None. **R. Shen:** None. **D.M. Dietz:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

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Topic: G.03. Motivation

Support: JSPS KAKENHI (21H00963, 22K18657, 22KJ2905, 24H00179)
Waseda University Grant for Special Research Projects (2022C-369, 2023C-350)

Title: Amygdala lesions alter the social approach of juvenile zebra finches during social learning

Authors: *T. G. FUJII, M. TANAKA;
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Abstract: The amygdala is known to play various roles in social behaviors in mammals. However, how the amygdala controls social behaviors to potentially modulate social learning remains to be understood. Here, we investigate the role of the amygdala in the social interactions of zebra finches, a songbird species that learns songs from adult tutors through social learning. While the nucleus taeniae, also known as the medial ventral arcopallium (AMV), is thought to contain a homologous region to a part of the mammalian amygdala, its function and neural circuits have not been fully explored in zebra finches. Immunohistochemistry identified that the AMV has a high density of parvalbumin-positive neurons compared to the adjacent arcopallium, a shared feature with the mammalian basolateral amygdala. Neuronal tracers injected into the AMV revealed its bidirectional connections with the hippocampus, as well as its projections to the midbrain, hypothalamic areas, and lateral septum, a part of the social behavior network. To identify its social function, the excitotoxin ibotenic acid was injected into the AMV in juvenile male zebra finches. In a social learning paradigm where juveniles were tutored by a series of two novel adult males on separate days, we analyzed their social interactions by using custom position-tracking software. Without AMV lesions, juvenile zebra finches gradually decreased

their approaching behavior toward the tutor over 3 days of continuous tutoring sessions. However, AMV-lesioned juveniles tended to continue approaching the tutor throughout the tutoring period. We also noted that AMV-lesioned juveniles were in closer proximity to the tutor than intact birds at the beginning of tutoring. Contrary to these differences in social approach behaviors, song learning was not significantly affected by AMV lesions. These results indicate the involvement of the amygdala in the regulation of inter-individual distances during social learning, although its precise role in social learning remains to be clarified.

Disclosures: T.G. Fujii: None. **M. Tanaka:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.19/O3

Topic: G.03. Motivation

Support: The Francis Crick Institute

Title: Identifying the Neural Circuitry Underlying Animal-Animal Attraction

Authors: *L. COCHRANE, X. CANO FERRER, L. KIMBLEY, A. SEGGEWISSE, A. IMBERT, M. WINDING;
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Abstract: Social behaviour is central to human and animal interactions, and its disruption is prevalent across neurodevelopmental disorders. Despite its significance, the neural circuitry governing social behaviour remains elusive, credited to the complex circuitry involved. To overcome this, we use the fruit fly *Drosophila* as a model to study social behaviour: the advanced genetic tools and recently reconstructed connectome enables the precise dissection of neural circuitries and genes imperative for social behaviour. This project aims to identify forms of attraction between *Drosophila* larvae and determine the neural circuits underlying such behaviour. For this purpose, we developed a custom-made behavioural recording device. We found that *Drosophila* larvae exhibit distinct attractive behaviours during development, with larvae initially displaying increased proximity to one another that reduces with age. Attractive behaviour was also modulated in the presence of food: food availability facilitated increased proximity and social interactions between conspecifics. In the future, we plan to selectively inactivate neurons based on the connectome to identify the circuits governing attractive behaviours. Thus, this project will uncover neural pathways underpinning animal-animal attraction and advance understanding of social development.

Disclosures: L. Cochrane: None. **X. Cano Ferrer:** None. **L. Kimbley:** None. **A. Seggewisse:** None. **A. Imbert:** None. **M. Winding:** None.

Poster

PSTR359: Motivation: Social Communication and Behavior I

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR359.20/O4

Topic: F.01. Neuroethology

Support: NASA grant 80NSSC17K0060
NASA grant 80NSSC21K0814
NIH grant MH107945
NASA-TRISH grant NNX16AO69A-P0402
UPenn Radiation Oncology pilot grant
Penn Provost/CHOP Academic Fellowship for Diversity in Science

Title: Whole-body exposure to space radiation (^{56}Fe) impairs stress-mediated social conflict behavior and alters social brain networks differently in male and female mice

Authors: *F. KIFFER[1], A. HAMANDI[2], N. JOHNSON[3], D. H. GUEZ-BARBER[1], S. YUN[4], A. J. EISCH[5];
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Abstract: Astronauts venturing to Mars will be subjected to unavoidable energetic charged particles comprising galactic cosmic rays. Previous work utilizing ground-based rodent exposures to energetic charged-particles shows that whole-body Mars mission-relevant doses alter numerous cognitive processes, including social memory, and sociability. A number of astronaut psychosocial stressors have been identified (confinement, distance from earth, communication delays) but the risk of charged-particle radiation as a psychosocial stressor is unknown. To this end, 6-month-old male and female C57Bl/6J mice were exposed to either sham irradiation (Sham) 3 x 6.7Gy fractions of ^{56}Fe (600 MeV/n; 56Fe IRR). Nine months later, one group of lifelong cagemates (Chronic TT) repeatedly underwent the tube dominance test (round-robin format) to assess social conflict and hierarchical behavior. Mice were subsequently tested for anxiety, sociability, social novelty, and despair response. A parallel group of lifelong cagemates (Acute TT) were kept behaviorally naive until 12 months post-exposure until one day of tube testing (3 rounds). Their brains were collected 90min after the last TT round. Whole brain cFos+ cell number was quantified and co-registered with the Allen Brain Atlas for network analysis. In the Chronic TT group, ^{56}Fe IRR male mice took more days to reach rank criteria, had lower rank stability, and spent a higher proportion of their behavior in touch-based conflict vs Sham male mice without a difference in trial duration. In contrast, ^{56}Fe IRR female mice took fewer days to reach rank criteria and had higher rank stability vs. Sham female mice; notably the proportion of different behaviors performed on each day did not differ between ^{56}Fe IRR and Sham IRR. In the Acute TT group, preliminary analysis suggests fewer cFos+ cells throughout the brain of male ^{56}Fe IRR vs. male Sham mice. These data suggest a fractionated 20cGy whole-body exposure to ^{56}Fe alters social conflict behavior in a sex-specific manner, which may be due

to lower neuronal activation in key brain regions associated with social dominance behavior. More broadly, we show that space radiation is a risk to the social domain, which warrants further investigation.

Disclosures: F. Kiffer: None. **A. Hamandi:** None. **N. Johnson:** None. **D.H. Guez-Barber:** None. **S. Yun:** None. **A.J. Eisch:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.01/O5

Topic: G.05. Mood Disorders

Support: CIHR Grant

Title: 5-ht1a biased agonist nlx101 elicits a rapid-acting antidepressant response in a genetic model of fluoxetine-resistant mice

Authors: *F. VAHID-ANSARI[1], A. NEWMAN-TANCREDI[2], A. F. FUENTES ALVARENGA[3], M. DAIGLE[3], P. R. ALBERT[4];
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Abstract: Major depressive disorder is a leading cause of disability worldwide and selective serotonin-reuptake inhibitors (SSRIs) are first-line treatment, but have a low remission rate. In order to address this issue, we have used cF1ko mice to knockout the 5-HT1A gene repressor Freud-1/CC2D1A in adult 5-HT neurons, resulting in over-expression of 5-HT1A autoreceptors, reduced 5-HT activity and a fluoxetine-resistant anxiety- and depression-like phenotype. We hypothesized that preferential targeting of post-synaptic cortical 5-HT1A heteroreceptors using the biased agonist, NLX-101 (F15599), would induce an antidepressant response. cF1ko mice were treated with repeated injections of NLX-101 (0.2 mg/kg, 5 intraperitoneal injections) 1-hour prior to each behavioral test (five tests in two weeks). This dose of NLX-101 did not elicit a hypothermic response, indicating lack of 5-HT1A autoreceptor activation. NLX-101 improved depression-like behavior in the forced-swim test, while inducing an anxiogenic-like response in elevated plus maze, open field and novelty-suppressed feeding tests. At 1 hr post-treatment, NLX-101 increased c-fos+/DAPI+ cells in prefrontal cortex and dorsal raphe. Immunostaining for SERT in cF1Ko mice showed significant reductions in 5-HT axonal volume and varicosity density in the prefrontal cortex, hippocampus, amygdala, and dorsal raphe and NLX-101 reversed these changes to wild-type levels. These results suggest that 5-HT projections are dynamic, in that hypoactivity of 5-HT neurons reduces 5-HT innervation, which can be rescued by NLX-101. Thus, acute treatment with NLX-101 mediates rapid antidepressant-like effects in fluoxetine-resistant cF1ko mice, an effect involving activation of prefrontal cortical-raphe connectivity.

Disclosures: F. Vahid-Ansari: None. **A. Newman-Tancredi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Employee and Stockholder of Neurolixis. **A.F. Fuentes Alvarenga:** None. **M. Daigle:** None. **P.R. Albert:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.02/O6

Topic: G.05. Mood Disorders

Support: NIMHANS
UGC

Title: Transcutaneous auricular vagus nerve stimulation (taVNS) ameliorates depression-like behavior by altering neurotransmitter levels in prefrontal cortex and amygdala

Authors: *K. S. SANGHMITRA[1], B. N. SRIKUMAR[2], B. SHANKARANARAYANA RAO[3], D. YOGANARASIMHA[4];
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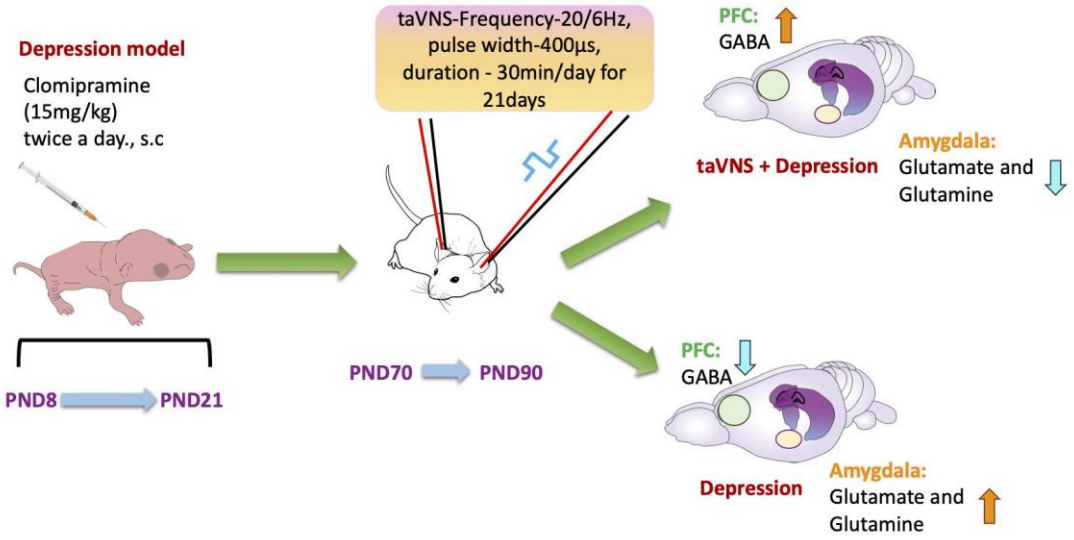
Abstract: Major depressive disorder (MDD) is a debilitating psychiatric illness characterized by low mood, anhedonia and suicidality. There are multiple hypotheses for the pathogenesis of MDD, but all of them converge at a common feature of altered neurotransmission. Transcutaneous auricular vagus nerve stimulation (taVNS) is shown to improve the mood and cognition in MDD. While there is some evidence for the role of Vagus nerve stimulation (VNS) on amino acid neurotransmission in depressive patients, there are limited studies on the effect of taVNS in depression. Accordingly, in the current study, we investigated the neurochemical alterations associated with the taVNS in an animal model of depression induced by neonatal clomipramine administration. To develop the model, 15mg/kg of clomipramine was subcutaneously injected into male Wistar rat pups twice a day from Postnatal day (PND)8 -21 while the control group received saline. taVNS with an alternating frequency of 20Hz/6Hz every 3 seconds and pulse width of 400μs was delivered 30 minutes daily for 21 days via bilateral electrodes placed at the concha region from PND70-90. Rats in the sham group did not receive any stimulation. Following stimulation, the prefrontal cortex and amygdala were micro-dissected from the whole brain. Analysis of amino acid neurotransmitter levels was performed by reversed-phase High-performance liquid chromatography. We observed elevated glutamate and glutamine levels in the amygdala of rats in the depression group and reduced GABA in the PFC. Subjecting the rats to taVNS decreased glutamate and glutamine levels in the amygdala and increased GABA levels in the PFC. Several studies have reported amygdalar hyperactivity and

PFC hypometabolism leading to disrupted cortico-amygdalar connectivity in MDD. Our findings indicate that 21 days of taVNS restores altered neurotransmitter levels in the PFC and amygdala in the depression group. These findings provide new insights into the antidepressant mechanisms of taVNS, which has implications for the treatment of depression and associated cognitive disorders.



(Figure created using images from Scidraw)

Disclosures: K.S. Sanghmitra: None. **B.N. Srikumar:** None. **B. Shankaranarayana Rao:** None. **D. Yoganarasimha:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.03/O7

Topic: G.05. Mood Disorders

Support: EIC-PATHFINDER 101070931

Title: Unveiling Dopamine Patterns in Depression Models: Deciphering Sex Differences with mfb-DBS parameters.

Authors: *L. MIGUEL TELEGA[1,2,3,4], V. A. COENEN[5,6,4,7], M. D. DOBROSSY[1,2,3,4,7];
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Freiburg, Freiburg im Breisgau, Germany; [4]Institute for Machine-Brain Interfacing Technology (IMBIT), Freiburg im Breisgau, Germany; [5]Dept. of Stereotactic and Functional Neurosurg., Univ. Med. Ctr. Freiburg, Freiburg im Breisgau, Germany; [6]Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany; [7]Center for Basics in Neuromodulation, Freiburg im Breisgau, Germany

Abstract: Superolateral medial forebrain bundle Deep Brain Stimulation (slMFB-DBS) has demonstrated rapid and long-term antidepressant effects in treatment-resistant depressive patients (TRD). However, understanding of its clinical efficacy is limited, and there is no clear consensus on parameter selection. Biophisically, the unmyelinated (dopaminergic) and myelinated neurons in the mfb (in rodent) would be recruited differently depending on the electrical current injected (chronaxie principle), usually with longer pulse widths. Therefore, excitability of the dopaminergic (DA) fibers, key regulating rewarding effects in the accumbal region, and innervated by the Ventral Tegmental Area (VTA), would potentially be different depending on parameter selection. The most recent studies have only demonstrated acute differential effects between healthy and depression models based on the pulse widths employed. Our study aimed to assess the immediate and long-term effects of various mfb-DBS parameters (including low and high frequencies and different pulse widths) on both tonic and phasic dopamine (DA) release in the nucleus accumbens. We used Fiber Photometry to measure DA activity and tested unilateral and bilateral stimulation in a spontaneous context, as well as bilateral stimulation during behavioral tasks. We studied the effects across experimental models: Sprague Dawley controls and Flinders Sensitive Line (FSL,depression-like model) in females and males (clinically relevant). Our results suggest reliable chronic DA readouts over all recording sessions to track mfb-DBS mediated effects. We were able to show: i.) mfb-DBS elicits an increased DA response with all parameters during stimulation, ii.) FSL animals seem to have different circuit dynamics compared to the Controls more specifically when using the clinically relevant parameters, where males show the most abrupt phasic increase compared to controls, and iii) differences in tonic activity pre- and post-DBS, and between spontaneous and behaving contexts. These findings will contribute to an improved understanding of the temporal and spatial dynamics of neurotransmitter release profiles, to understand the clinical effects of MFB-DBS, and potentially lead to a refinement of therapeutic DBS treatment strategies for depression, and other psychiatric disorders.

Disclosures: L. Miguel Telega: None. **V.A. Coenen:** None. **M.D. Dobrossy:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.04/O8

Topic: G.05. Mood Disorders

Title: Interferon-alpha administration in rats as a model capturing the Yin and Yang of depression: effects of acute ketamine.

Authors: *E. PASCHEN[1], J. KEALY[1], S. FARRELL[1], P. JAYABAL[1], R. AGRAWAL[2], R. M. MEYER[3], M. BIANCHI[1];
[1]Ulysses Neurosci. Ltd., Dublin, Ireland; [2]Delix Therapeut., Bedford, MA, ; [3]Delix Therapeut., Boston, MA.

Abstract: Interferon-alpha (IFN-alpha) is an endogenous cytokine that is used to treat cancers and viral infections in humans. However, up to 48% of IFN-alpha treated patients develop depressive symptoms, which are usually treatable with chronic treatment with SSRIs. These behavioural and inflammatory effects are back-translatable to rats as a neuroinflammatory model of depression. IFN-alpha is hypothesised to exert inflammatory effects by binding to the IFNAR1 and 2 receptors, resulting in activation of STAT, MAPK/ERK and PI3K signalling cascades. In addition to these, we show that chronic IFN-alpha treatment in rats also produces a molecular profile consistent with impairments in neuroplasticity. Male Wistar rats were treated with IFN-alpha (170,000IU/kg, SC) or saline (0.9%, SC) three times per week for four weeks. Wistar-Kyoto (WKY) rats were included as a comparison group. Rats underwent a battery of behavioural and molecular testing and a cohort of animals underwent electrophysiological recordings. Animals treated with IFN-alpha show central decrease in p-Akt in the hippocampus, indicating central engagement of the STAT neuroinflammatory pathway. There is also a more generalised central and peripheral neuroinflammatory response with increases in TNF-alpha and IL-6. IFN-alpha-treated rats do not show sickness behaviour, but have depressive-like alterations including increase in Forced Swim Test (FST) immobility paralleled by central decrease in synaptic (SV2a and PSD-95) markers as well as central and peripheral increase in acetylated alpha-tubulin (Acet-Tub), a marker of less dynamic microtubules. IFN-alpha-treated rats receiving acute ketamine (5 mg/kg, SC) show rescue of FST immobility, inflammatory markers, synaptic markers and Acet-Tub. EEG recordings were also altered in IFN-alpha animals and affected by ketamine administration. WKY rats showed similar behavioural, molecular and neurophysiological data. IFN-alpha-induced pathology resembles both the Yin (inflammation) and the Yang (altered neuroplasticity) of depression and ketamine rescues both aspects. Thus, the IFN-alpha model is a valuable model of depression-like symptomatology to test novel antidepressant compounds.

Disclosures: E. Paschen: None. **J. Kealy:** None. **S. Farrell:** None. **P. Jayabal:** None. **R. Agrawal:** None. **R.M. Meyer:** None. **M. Bianchi:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.05/O9

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Warner Fermaturo Grant 560-760

Title: Dissociative Effects of Ketamine in Juvenile Rats

Authors: *D. MIDDLEMAS, A. M. KLINNER;
Pharmacol., KCOM/ATSU, Kirksville, MO

Abstract: Dissociative Effects of Ketamine in Juvenile Rats: Dose Impact & Duration
Problem: The use of a single sub-anesthetic dose of ketamine has shown rapid and sustained antidepressant effects in adult humans and rats, but concerns about abuse due to dissociative properties persist. This study investigates the dissociative effects of ketamine in female juvenile rats. The aim is to assess the impact and duration of these effects at subanesthetic doses.
Methods: Female Sprague-Dawley rats (27 ± 2 days old) received sub-anesthetic doses of ketamine or saline via intraperitoneal injection. Observations were conducted at various time points over 120 minutes post-injection. Three blinded observers independently tallied each behavior category. The dissociative index, representing the normalized difference between total dissociative and non-dissociative behaviors, was calculated, and plotted over time for each dose.
Results: Dissociative behaviors were evident two hours post-injection, decreasing significantly between one- and two hours post-injection. The 60 mg/kg dosage exhibited variability in the observed dissociative behavior time course among three observers. Circling was the most prevalent dissociative behavior observed at 40 and 60 mg/kg doses.
Conclusion: Data suggest that higher ketamine doses elicit dissociative behaviors two hours post-injection. Categorizing dissociative versus non-dissociative behaviors becomes more challenging at higher doses, emphasizing the importance of potentially extending the two-hour monitoring window after ketamine administration as a rapid-acting antidepressant in adolescents humans.

Disclosures: D. Middlemas: None. **A.M. Klinner:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.06/O10

Topic: G.05. Mood Disorders

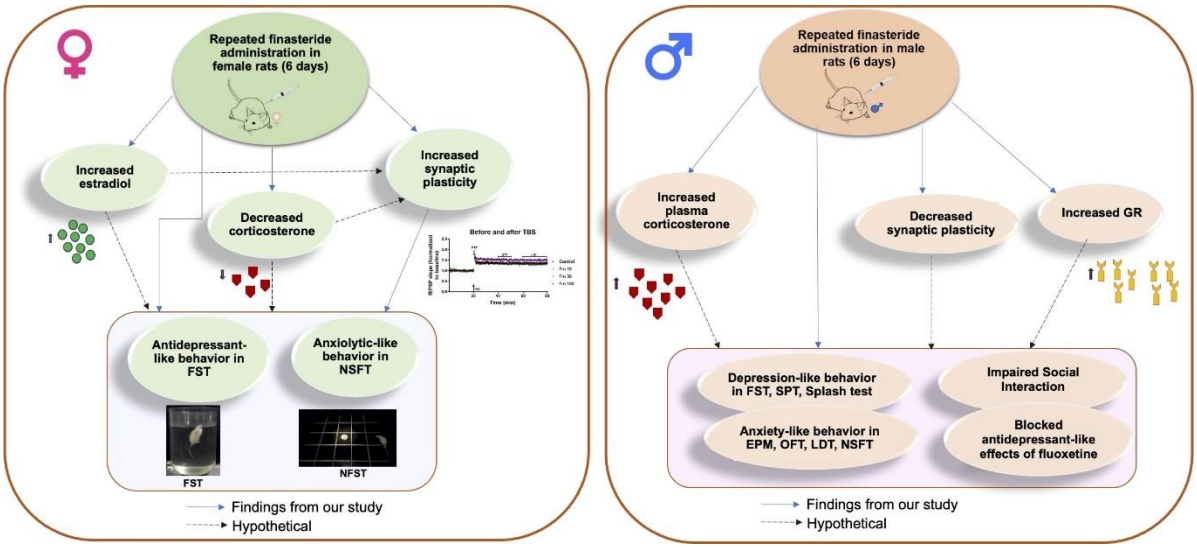
Support: DST-SERB (ECR/2015/000545; CRG/2020/005229)
CSIR, India
NIMHANS Intramural grant (NIMH/Proj/BNS/00555)
Dr. Reddy's lab for the finasteride gift sample

Title: The potential role of glucocorticoids in the sexually dimorphic effects of short-term finasteride administration on depression- and anxiety-like behavior and synaptic plasticity

Authors: S. BEDADALA[1], N. JOSE[2], B. SHANKARANARAYANA RAO[1], ***B. N. SRIKUMAR**[1];
[1]Neurophysiol., Natl. Inst. of Mental Hlth. and Neuro Sci. (NIMHANS), Bengaluru, India;

[2]Neurophysiol., Natl. Inst. of Mental Hlth. and Neuro Sci. (NIMHANS), Thiruvananthapuram, India

Abstract: One of the key enzymes responsible for the neurosteroid production is 5alpha-Reductase (5alpha-R) catalyzes a rate-limiting step. We examined the effects of short- -term 5alpha-R inhibition using finasteride on depression and anxiety in male and female rats. We subjected male Wistar rats to repeated finasteride administration (10, 30 or 100 mg/Kg, s.c.) over a period of 6 days. We evaluated depression and anxiety-like behaviour in several paradigms. Short-term finasteride administration at 100 mg/Kg. s.c. resulted in increased immobility in the forced swim test, decreased grooming in the splash test, decreased sucrose preference and impaired social interaction. Further decreased open arm exploration in the elevated plus maze, decreased time spent in the centre in the open field test, decreased time spent in the light chamber in the light-dark test, and increased latency to feed in the novelty suppressed feeding test were observed. Further, the antidepressant effect of fluoxetine was diminished following finasteride administration. In female rats, we observed that finasteride administration decreased total immobility duration in FST, indicating antidepressant-like effect and decreased the latency to first bite in NSFT, showing anxiolytic-like effect. Interestingly, ex-vivo field potential recordings in the Schaffer Collateral-CA1 synapses showed that hippocampal LTP is impaired in male rats while it is enhanced in female rats. Further, corticosterone levels were elevated in male rats and decreased in female rats, following 6 days of finasteride administration. These results indicate interesting but contrasting effects of finasteride on male and female rats. Further research in this area has potential for development of novel neurosteroid-based therapeutics to treat neuropsychiatric diseases.



Disclosures: S. Bedadala: None. **N. Jose:** None. **B. Shankaranarayana Rao:** None. **B.N. Srikumar:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.07/O11

Topic: G.04. Emotion

Support: Department of Psychology

Title: Observational and behavioral data from machine learning show that buprenorphrine alters anxiety-like behavior in C57BL/6J mice

Authors: O. SHARMA[1], M. J. MYKINS[3], G. J. O'CONNOR, Jr.[2], B. LOWERY[1], *H. A. BAGHDOYAN[1], R. LYDIC[1];
[1]Psychology, [2]Biomed. Engin., Univ. of Tennessee, Knoxville, TN; [3]Inst. for Cell Engin. and Neurol., Johns Hopkins Med. Institutions, Reisterstown, MD

Abstract: Buprenorphine is an opioid approved for treating opioid use disorder (https://tinyurl.com/avamt97a). Buprenorphine also contributes to the treatment of human depression (10.3390/ijms19082410) and anxiety (10.4103/0253-7176.211765) and decreases depression and anxiety-like behaviors in male mice (10.1007/s00213-014-3723-y). Human anxiety and depression are associated with obesity and being female (10.1016/j.tem.2021.10.005). The forgoing findings encouraged the present study to test the hypothesis that sex and obesity alter the effects of buprenorphine on anxiety-like behavior in mice. These IACUC approved studies used B6 mice comprised of adult males (n=10), females (n=10), and males with diet-induced obesity (DIO, n=10). Mice received subcutaneous injections (0.3 mL) of saline (control) and buprenorphine (1 and 10 mg/kg). After each injection mice were placed on an elevated zero maze (EZM) for 5 min and their behavior was recorded via digital video. The EZM consists of two open and two closed regions of equal area. As a prey species, mice prefer the EZM closed region. Potential threats and approach-avoidance conflicts evoke anxiety in humans (10.1523/jneurosci.2732-19.2020) and anxiety-like behaviors in mice (https://www.ncbi.nlm.nih.gov/books/NBK5221/). Stretch attend postures and head dips (SA and HD) are anxiety-like behaviors observed when mice explore EZM open regions and approach the ledge of the elevated maze. After each of the 90 injections the videos were scored for frequency of SA and HD behaviors. Videos were also uploaded to the cloud, and mouse behaviors were quantified via open-source programs (Google Colab, DeepLabCut, and SimBA) and machine learning. The results show that relative to saline, buprenorphine decreased SA and HD behaviors in all three mouse groups. Two-way, repeated measures ANOVA of HD and SA postures revealed main effects due to buprenorphrine dose ($P<0.0001$), mouse group ($P<0.0001$), and a group by dose interaction ($P=0.0056$). Eta-squared values for the buprenorphrine dose effect=0.22, mouse group effect=0.27, and for the dose by group interaction=0.12. The SA and HD results concur with machine learning analyses revealing that buprenorphine altered anxiety-like behaviors including time spent in the EZM open region, distance traveled, and running speed (Sharma et al in press, https://jpet.aspetjournals.org/, 2024). Considered together, the results support the conclusion that the effects of buprenorphine on anxiety-like behaviors in congenic B6 mice vary as a function of diet-induced obesity and sex.

Disclosures: O. Sharma: None. **M.J. Mykins:** None. **G.J. O'Connor:** None. **B. Lowery:** None. **H.A. Baghdoyan:** None. **R. Lydic:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.08/O12

Topic: G.04. Emotion

Support: RCMI Grant U54-MD007600 NIMHD-NIH
NINDS R21NS119991
COBRE II P20 GM103642
Neuro-ID 2R25NS080687

Title: Effects of antibiotics on avoidance behaviors in rats

Authors: *H. HADDOCK-MARTÍNEZ[1], L. L. MENDEZ-SANTACRUZ[2], N. JIMENEZ-RIVERA[3], T. SALCEDO[4], D. SIERRA-MERCADO[5], O. MARTÍNEZ GUZMAN[6];
[1]Biol., Univ. de Puerto Rico, Rio Piedras, San Juan, Puerto Rico; [2]Biol., Univ. of Puerto Rico, San Juan, Puerto Rico; [3]Univ. Puerto Rico Sch. of Med., San Juan, PR; [4]Univ. of Puerto Rico Bayamon campus, Bayamon, PR; [5]Anat. & Neurobio., Univ. Puerto Rico Sch. of Med., San Juan, Puerto Rico; [6]Microbiology and Med. Zoology, Univ. of Puerto Rico Sch. of Med., San Juan, PR

Abstract: Antibiotics are crucial in the treatment of infectious diseases and are frequently prescribed in an oral format. Unfortunately, oral antibiotics cause dramatic alterations in gut microbial composition. Here, we will evaluate the behavioral effects of changes in gut microbiota composition due to oral broad-spectrum antibiotics. We hypothesize that consumption of oral antibiotics mixture-drinking water will increase avoidance behaviors and lead to changes in brain activity and gut microbiota composition. Specifically, rodents will consume either the oral antibiotics mixture in drinking water (equal amounts of ampicillin, streptomycin, and clindamycin at a concentrations of 1mg/kg) (n=16), or filtered water as a control (n=16), and then be assessed for effects on avoidance and anxiety behaviors, as well as activity in brain regions implicated in avoidance. Animals exposed to antibiotics spent more time on the platform throughout the test session during the tone ($p=0.0402$). Also, animals exposed to antibiotics spent less time in the center and show a higher anxiety index in the open field test ($p=0.0190$) and elevated plus maze ($p=0.0266$) respectively. Finally, preliminary results of c-Fos labeling shows an increase in (nucleus accumbens) NaC and (basolateral amygdala) BLA brain regions. These data suggest that alteration in gut bacteria due to antibiotics increases avoidance behaviors and anxiety-like behaviors. The preliminary results of c-Fos labeling shows an increase in NaC and BLA brain regions corresponds to the increased avoidance behaviors as we observed by spending more time on the platform during the tone. The translational relevance of this work suggests that antibiotics may contribute to mental health disorders, since excess avoidance is characteristic of patients with fear and anxiety disorders.

Disclosures: H. Haddock-Martínez: None. **L.L. Mendez-Santacruz:** None. **N. Jimenez-Rivera:** None. **T. Salcedo:** None. **D. Sierra-Mercado:** None. **O. Martínez Guzman:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.09/O13

Topic: F.03. Stress and the Brain

Support: R15DK121246

Title: Chronic Oral Administration of Microcystin Elevates Body Temperature Without Altering Body Composition in Mice

Authors: C. M. BLANK[1], S. GHAJU[2], E. WELCH[3], X. MOU[1], W. C. CHUNG[3], *C. M. NOVAK[1];
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Abstract: Cyanobacteria, commonly known as blue-green algae, are a prevalent public health concern found in many freshwater sources, including the Great Lakes. Lake Erie, a fresh water source for nearly 12 million people, is the shallowest of the five Great Lakes, making it rich in nutrients that drive excessive growth of blue-green algae, leading to the development of harmful algal blooms (HABs). One of the most common species of cyanobacteria found in Lake Erie HABs is *Microcystis aeruginosa*, which produces the toxin microcystin. Microcystin is a known hepatotoxin in humans, and pre-clinical *in vivo* studies have shown effects on other organ systems and tissues including the kidney, heart, lungs, reproductive system, nervous system, and the immune system. New evidence suggests an impact on neural centers affecting the stress axis and potentially energy balance. Here, we implanted male and female mice with a temperature transponder (intraperitoneal) and administered a low dose of microcystin or water orally every other day for 22 days. After administration, we measured body temperature non-invasively at 15-minute intervals for 1 hour, and then again at 2 hours, 4 hours, 8 hours, and 24 hours. We measured body weight daily as well as lean and fat mass using EchoMRI prior to the onset of microcystin treatment and again on day 22 to assess changes in body composition. Our results demonstrate that chronic exposure of mice to microcystin did not significantly alter body weight or composition. However, there was a significant elevation in body temperature in microcystin-treated mice compared to controls. This increase in core temperature was observed immediately following administration of microcystin and persisted through the following 24-hour period. This indicates a possible immune response that could lead to other physiological consequences, such as changes in metabolism via stress-response mechanisms. Further research is warranted to explore the broader implications of the observed effects on neural centers, stress axis, and thermoregulatory control.

Disclosures: C.M. Blank: None. **S. Ghaju:** None. **E. Welch:** None. **X. Mou:** None. **W.C. Chung:** None. **C.M. Novak:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.10/O14

Topic: G.05. Mood Disorders

Support: National Fellowship and Scholarship for Higher Education of ST Students

Title: Neuroprotective potential of Hedychium coronarium essential oil in wistar rats: in silico, in vitro and in vivo study

Authors: *A. KISKU, K. SULAKHIYA;
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Abstract: Abstract Inflammation and oxidative stress result in neuropsychiatric disorders (NDs). Tryptophan breakdown and activation of the kynurenine pathway may be brought on by pro-inflammatory mediators. In India, China and Vietnam, *Hedychium coronarium* Koen. (Zingiberaceae) is traditionally used as folk medicine to treat a range of illnesses, including eye disorders. The primary goal of this study is to investigate the neuroprotective effect of HCEO on the basis of *in silico*, *in vitro* and *in vivo* analysis using molecular docking, behavioral analysis and biochemical analysis in animal models. Hydrodistillation was used to extract the essential oils, and gas chromatography coupled to mass spectrometry (GC-MS) was used to analyse the results. The 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay was used to quantify *in vitro* antioxidant activities, and the anti-inflammatory activities were evaluated using the protein denaturation method. Behavioral paradigms such as elevated plus maze (EPM), forced swim test (FST) and Novel object recognition test (NORT) were employed to assess neuropsychiatric behavior in rats. Hippocampal cytokines, MDA and GSH levels were measured. The primary constituents identified in this study by GC-MS in the EO were monoterpenes linalool (31.21%) and 1, 8-cineole (25.72%), comprising 56.93% of total oil compounds. The essential oils exhibited significantly increased ($P< 0.05$) antioxidant activity. Moreover, it also showed significantly increased ($P< 0.05$) anti-inflammatory activity. Docking results support the significant target-drug interaction. Essential oil treatment may ameliorate stress-induced neuroinflammation by reducing ($P<0.05$) brain IL-1β, TNF-α levels, and oxidative & nitrosative stress by free radical scavenging. In conclusion, the results suggest that HCEO prevented stress-induced NDs, which may be governed by inhibiting pro-inflammatory and inflammatory cytokine production and oxidative stress levels. The results support the potential usefulness of HCEO in the treatment of neuropsychiatric disorders such as anxiety, depression, and cognitive dysfunction associated with inflammation and oxidative stress.
Keywords: Essential oil, molecular docking, neuroinflammation, DPPH assay, protein denaturation, behavioral analysis

Disclosures: A. Kisku: None. **K. Sulakhiya:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.11/O15

Topic: G.05. Mood Disorders

Support: Pharmacy Alumni Centennial Research Endowed Chair award , Ohio Norther University

Title: Differential affective behavioral responses to medications targeting monoamine transmission in male and female mice lacking either RGS2 or RGS4

Authors: H. MATSUI[1], S. SEELEY[1], ***M. D'SOUZA**[2,3];
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Abstract: Regulator of G protein-signaling (RGS) proteins 2 and 4 proteins negatively modulate signaling pathways of G protein-coupled receptors (GPCRs), which play an important role in mediating the effects of monoamine neurotransmitters such as dopamine, norepinephrine, and serotonin. These neurotransmitters in turn play an important role in the action of currently available antidepressant and anxiolytic medications. The overall objective of the study was to assess the acute behavioral effects of currently used antidepressants and anxiolytics in male and female mice lacking either RGS 2 or 4 and their wildtype counterparts. Anxiety-like behaviors were assessed using the elevated plus maze and antidepressant-like effects were assessed using the tail suspension test. The anxiolytic and antidepressant drugs evaluated in this study included those that primarily target monoamine neurotransmission such as fluoxetine (30 mg/kg), desipramine (30 mg/kg), and buspirone (3 mg/kg). Antidepressant-like effect of fluoxetine was seen in both male and female mice lacking RGS2 compared to respective saline controls. In contrast, antidepressant-like effect of fluoxetine was attenuated in female, but not male mice lacking RGS4 compared to respective saline controls. Antidepressant-like effect of desipramine was attenuated in both male and female mice lacking RGS2 compared to wildtype controls. In contrast, antidepressant-like effect of desipramine was attenuated in female mice, but not male mice lacking RGS4 compared to respective saline controls. Anxiolytic-like effect of buspirone was observed in male mice lacking either RGS2 or RGS4 compared to respective saline controls. In contrast, anxiolytic-like effect of buspirone and fluoxetine was attenuated in female mice lacking RGS2 compared to respective saline controls. Together, the data suggest RGS2 and RGS4 sex-dependently differentially influenced affective responses to tested antidepressant and anxiolytic medications. Currently, we are evaluating molecular and neurochemical mechanisms underlying the above described behavioral effects in male and female mice lacking either RGS2 or RGS4. Data obtained from these studies will help in understanding the anxiolytic and

antidepressant effects of drugs in humans carrying polymorphisms of the RGS2 and RGS4 genes.

Disclosures: H. Matsui: None. **S. Seeley:** None. **M. D'Souza:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.12/O16

Topic: G.05. Mood Disorders

Support: USAMRAA Contract # HT94252320003

Title: A pacap analogue prevents LHb dysfunction and motivational deficits following mild traumatic brain injury in mice

Authors: E. THOMAS[1], L. SZABO[2], W. FLERLAGE[3], C. APOSTOL[2], T. E. SMITH[2], S. GOUTY[4], B. M. COX[5], R. POLT[6], *F. NUGENT[3];
[1]Pharmacol. and Mol. Therapeut., 1Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD; [2]Univ. of Arizona, Tucson, AZ; [3]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD; [4]Uniformed Services Univ., Bethesda, MD; [5]Brian Cox, Rockville, MD; [6]Chem. & Biochem., The Univ. of Arizona, Tucson, AZ

Abstract: The vast majority of traumatic brain injury are mild (mTBI). Incidence rates of mTBI within the United States have risen over the last decade, with the most at-risk populations being contact-sports athletes, military personnel, and victims of domestic abuse. Stress-related disorders are frequently present and have a potentially life-threatening impact on mTBI patients' quality of life and perceived symptom severity. Enhancing the pituitary adenylate cyclase-activating polypeptide (PACAP) in the brain is shown to exert neuroprotective and neurotrophic effects in pathological conditions associated with PACAP deficiency such as aging, neurodegenerative disorders as well as traumatic brain injury but whether PACAP can also provide neuroprotection on the negative effects of mTBI in mood-related brain circuits and associated affective and emotional dysregulation is unknown. In this study, we tested the preventive efficacy of a novel PACAP agonist with enhanced stability and blood brain barrier penetration on long-term negative effects of mTBI on social and motivated behaviors through regulation of lateral habenula (LHb) activity (a critical brain region involved in pathophysiology of psychiatric illnesses including depression and anxiety) in male mice. Using an established preclinical repetitive closed head mouse model of mTBI in mice, we confirmed that mTBI resulted in LHb hyperexcitability in male mice a month after the injury. Moreover, our preliminary results show potential efficacy of the PACAP analogue in prevention of mTBI-induced LHb hyperexcitability and motivational deficits in self-care grooming behavior in sucrose splash test. Our preclinical study has the potential to provide translational validity for the

use of the novel PACAP agonists in prevention of mTBI-related reward circuit dysfunction and depression.

Disclosures: E. Thomas: None. **L. Szabo:** None. **W. Flerlage:** None. **C. Apostol:** None. **T.E. Smith:** None. **S. Gouty:** None. **B.M. Cox:** None. **R. Polt:** None. **F. Nugent:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.13/O17

Topic: G.05. Mood Disorders

Support: NIMH Grant 5250119201

Title: Determining the molecular and circuit mechanisms that underly ketamine's fast acting antidepressant action to guide improved treatment.

Authors: *A. AREFIN[1], H. MUNGUBA[2,3], R. HASEGAWA[4], J. LEVITZ[2,3], C. M. LISTON[5]; [1]Biochem., Weill Cornell Med. Col., New York, NY; [2]Biochem., Weill Cornell Med., NYC, NY; [3]Psychiatry, Weill Cornell Medicine, New York, NY; [4]Psychiatry, Weill Cornell Med., New York, NY; [5]Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: Dysregulation of neural circuits often leads to symptoms that are associated with psychiatric diseases, such as depression. While therapeutic approaches have typically been based on the serendipitous identification of symptom-alleviating compounds, a deeper understanding of the mechanisms underlying the pathophysiology and treatment of depression is needed to guide the development of new therapeutics. Ketamine has been shown to be an antidepressant (AD) with rapid onset and sustained efficacy in patients resistant to other treatments; however, the underlying mechanisms of this action remain poorly understood. In this study, we aimed to identify key molecular and synaptic triggers involved in ketamine’s antidepressant action and harness these mechanistic findings to guide improved pharmacological treatments. We first find that the behavioral effects of ketamine rely on agonism of mu-opioid receptors (MORs), which are enriched in somatostatin-expressing interneurons (Sst^+ INs) in the medial prefrontal cortex (mPFC). We then use a battery of genetic and photopharmacological tools to find that Gi/o signaling in mPFC SST+ INs is necessary for antidepressant-like effects induced by ketamine and sufficient to elicit antidepressant-like behavioral responses. We also find that Sst+ INs are highly sensitive to chronic stress which leads to a unique presynaptic hypertrophy phenotype which is reversed by ketamine. Motivated by these findings, we used RNA-sequencing to identify several mPFC SST+ IN-enriched GPCRs as potential, novel AD targets. Finally, synergistic pharmacological targeting of multiple GPCRs enriched in SST+ INs enabled a more efficacious AD-like behavioral response with reduced motor and anxiety-like side effects compared to ketamine. Together, our study provides a novel framework merging mechanistic

insights with genetics-based identification of new GPCR targets, paving the way for enhanced treatment strategies for psychiatric disorders.

Disclosures: A. Arefin: None. **H. Munguba:** None. **R. Hasegawa:** None. **J. Levitz:** None. **C.M. Liston:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.14/O18

Topic: G.05. Mood Disorders

Support: Ministry of Science and Technology of China Grant STI2030-Major Projects 2021ZD0202900
National Natural Science Foundation of China Grant 32170960

Title: Excitatory neurons in the Orbitofrontal Cortex mediated the anti-depressant effect of psilocybin

Authors: *Z. HUANG[1], W. ZHANG[2];
[2]Nat. Inst. on Drug Dependence, [1]Peking Univ., Beijing, China

Abstract: Recently, psilocybin has been proposed as a novel medication for psychological disorders, clinical advances show its promising roles in the treatments of depression, addiction, and obsessive-compulsive disorder. Psilocybin is a psychedelic whose metabolite, psilocin, an agonist of 5-HT_{2A} receptor, which activates Gαq and β-arrestin signaling pathways and then lead to downstream effects. It is suggested that psilocybin induced plasticity changes in neurons, such as increase of spines of excitatory neurons. Meanwhile, the underlying mechanisms for the anti-depressant effect of psilocybin are not fully illustrated, and in the orbitofrontal cortex (OFC), a brain region vulnerable to brain disorders such as depression, its effects are not fully understood. Here, we combined single-nucleus RNA-seq with functional assays to study the long-term effects of psilocybin on the OFC. We demonstrated that a single dose of psilocybin induced long-term genetic and functional changes in excitatory neurons in the OFC, which reduced activity of the brain region. Knockdown of 5-HT_{2A} receptor in deep layer excitatory neurons abated psilocybin-induced functional changes and the anti-depressant effect. Together, these results showed the excitatory neurons in the orbitofrontal cortex mediate the mechanism for the anti-depressant effect of psilocybin.

Disclosures: Z. Huang: None. **W. Zhang:** None.

Poster

PSTR360: Animal Models of Therapeutics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR360.15/O19

Topic: G.05. Mood Disorders

Support: NIMH 1R01MH132789-01A1
Grant from Hope for Depression Research Foundation

Title: Deep brain stimulation induces white matter remodeling and functional changes to brain-wide networks

Authors: *S. H. FUJIMOTO[1], A. FUJIMOTO[2], C. ELORETTE[3], A. SELTZER[3], E. ANDRAKA[3], W. G. JANSSEN[4], D. FOLLONI[4], K. CHOI[5], B. E. RUSS[6], H. S. MAYBERG[7], P. H. RUDEBECK[1];
[1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Dept. of Neurosci., [4]Neurosci., [5]Radiology / Neurosurg., [3]Icahn Sch. of Med. at Mount Sinai, New York, NY; [6]Ctr. for Biomed. Imaging and Neuromodulation, Nathan Kline Inst., Orangeburg, NY; [7]Ctr. for Advanced Circuit Therapeut., Mount Sinai, New York, NY

Abstract: Introduction: Deep brain stimulation targeting subcallosal anterior cingulate cortex and adjacent white matter (SCC-DBS) is a promising therapy for treatment resistant depression (TRD). However, little is known about the anatomical and functional mechanisms that underlie this therapy. Thus, the aim of this study was to establish how SCC-DBS works in healthy brains, focusing on determining the brain-wide network-level anatomical and functional effects of white matter stimulation. **Methods:** Modeling the approach used to successfully treat TRD patients, we implanted SCC- DBS electrodes in two rhesus macaques. Specifically, we identified the confluence of the cingulum bundle, forceps minor, and uncinate fasciculus using diffusion tractography imaging (DTI). We then implanted a DBS lead unilaterally in this location, the other hemisphere serving as a control. One month after electrode implantation, stimulation (5mA, 130Hz, 90μsec) began and was maintained for 6 weeks. DTI and whole brain resting-state functional MRIs (rs-fMRIs) were acquired before electrode implantation and following 6 weeks of SCC-DBS stimulation to reveal the anatomical and functional effects of SCC-DBS. Fractional anisotropy (FA) was calculated from DTI data to investigate the macro-level anatomical white matter changes. Additionally, we investigated the micro-level structure changes by histological assessments using immunofluorescence staining of oligodendrocytes and electron microscopy analysis of myelin. Functional data were analyzed using a seed-based comparative-connectome approach where SCC-DBS stimulation induced changes in functional connectivity (FC) were determined. **Results:** Compared to before stimulation, we found that six weeks of chronic SCC-DBS enhanced white matter integrity in the midcingulate portion of cingulum bundle selectively. We corroborated this effect at the microscopic level, finding a significant increase in the numbers of oligodendrocytes and thickened myelin in the same region. Additionally, we also found that SCC-DBS significantly changed FC between stimulated SCC and multiple brain networks' hubs, mainly in the default mode network which is connected through the cingulum bundle. **Conclusion:** Our data reveal the specific effects of SCC-DBS showing that it causes myelin remodeling and brain network level functional changes both of which likely contribute to the therapeutic effects of this emerging neuromodulation approach.

Disclosures: S.H. Fujimoto: None. **A. Fujimoto:** None. **C. Elorette:** None. **A. Seltzer:** None. **E. Andraka:** None. **W.G. Janssen:** None. **D. Folloni:** None. **K. Choi:** F. Consulting Fees (e.g., advisory boards); Abbott Neuromodulation. **B.E. Russ:** None. **H.S. Mayberg:** F. Consulting Fees (e.g., advisory boards); Abbott Neuromodulation. **P.H. Rudebeck:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.01/Web Only

Topic: G.09. Drugs of Abuse and Addiction

Title: A systematic meta-analysis of the effects of cannabis use on driving, as assessed by the standard deviation of lateral position.

Authors: *N. TANNU[1], **O. TANNU**[2];
[1]Talkiatry, McKinney, TX; [2]Jordan High Sch., Katy, TX

Abstract: BACKGROUND: There has been an increasing trend of recreational use of cannabis secondary to legalization and along with medicinal use, there has been a bigger focus on the risks associated with driving under its influence. Tetrahydrocannabinol (THC) is considered the main psychotropic component that causes cognitive impairment, altering the sense of time, causing mood changes and problem-solving issues, motor and memory impairment, as well as psychosis. Many epidemiological studies show cannabis increases crash risk but the effects on driving are equivocal. A validated method used often for alcohol-induced driving impairment is the standard deviation of lateral position (SDLP) which is an index of lane weaving, swerving, and overcorrecting. **METHODS:** The literature review followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA) guidelines. The searched databases included MEDLINE, APA PsycInfo, Web of Science, and Ovid Embase for English. Only the peer-reviewed articles, that provided adequate data to calculate effect sizes were included in this study. The search was limited to studies published from the start of databases to February 2024. The search terms included cannabis, marijuana, and SDLP. The inclusion criteria for studies were (1) on-the-road driving tests, (2) placebo-controlled double-blind studies, (3) participants being healthy volunteers, and (4) volunteers who had not used other drugs. Data was extracted detailing study design, age (average of 28.9 years), sex (both males and females), number of participants (n=127), and outcome measure off SDLP with +/- 95% confidence interval (CI). **RESULTS:** The database search shows a paucity of research on this topic and resulted in twenty studies that were fully reviewed for quantitative analysis of which nine met the inclusion criteria. The continuous random effect model of meta-analysis described by Hartung, Knapp, Sidik, and Jonkman was used. We used the mean difference statistic as the measure of effect size. The resulting forest plot supported an association between cannabis use while driving and an increased SDLP (Mean difference- 2.711, 95% Lower CI of 1.683, and 95% Upper CI of 3.738, with P <0.001). **CONCLUSION:** Many reviews note that cannabis affects cognitive functioning especially if the onset of use is in adolescence and early adulthood. The present data show that

cannabis use significantly increases SDLP, a complex function of cognition, by 2.711 cm ($p<0.001$) in a population with an average age of 29. This is the first meta-analysis to show the detrimental effect of cannabis on SDLP an important driving performance measure.

Disclosures: N. Tannu: A. Employment/Salary (full or part-time):; Talkiatry. **O. Tannu:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.02/O20

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH R01AA030283

Title: Neurobehavioral mechanisms of psychotic-like experiences in cannabis users

Authors: *E. M. CAMPBELL, J. HOGEVEEN;
Dept. of Psychology, The Univ. of New Mexico, Albuquerque, NM

Abstract: Background: The causal nature of the relationship between cannabis use and psychosis is complex and still a subject of ongoing debate. Psychotic-like experiences (PLEs) may present an opportunity to better understand how cannabis use relates to these effects on the psychosis spectrum both acutely and broadly, with implications for informing mental health outcomes and better understanding potential neurobehavioral mechanisms underlying psychotic-like reactivity in particular individuals. **Methods:** 48 participants aged 13-21 completed the first session of a longitudinal study assessing substance use patterns, problematic cannabis use, PLEs, and neurobehavioral performances. **Results:** Regular cannabis users (n=13) were identified and compared with those who used had never tried cannabis or reported using cannabis less than monthly. Preliminary analysis showed that regular cannabis users reported a higher number of broad PLEs ($U = 134$, $p = .027$), and higher PLE-associated distress ($U = 135$, $p = .029$). In all individuals who had tried cannabis (n=29), retrospective reports of acute dysphoric PLEs to cannabis were positively associated with the Marijuana Problems Index (rho = .682, $p = .043$) and adverse childhood experiences (rho = 0.914, $p = .004$), while acute euphoric PLEs to cannabis was positively associated with monthly use frequency (rho = .728, $p = .028$). Regular cannabis users' fMRI activity during novelty salience processing will also be reported as a function of PLE frequency, as will analyses of the developmental trajectory of cannabis use and PLEs pending further data collection. **Conclusions:** These findings replicate prior work showing that regular cannabis users, particularly at younger ages, have a greater degree of broad distressing PLEs. Additionally, they show that different types of acute psychotomimetic responses relate to particular characteristics of cannabis use i.e., dysphoric experiences are increased in those with cannabis -related problems and trauma, while replicating prior findings on the association between euphoric experiences and frequency of use. Future analyses of these data will account for additional covariates of the PLE-cannabis relationship e.g.,

psychopathological variables like anxiety and depression, and will analyze neurobehavioral mechanisms underlying these relationships and their developmental trajectories.

Disclosures: E.M. Campbell: None. **J. Hogeveen:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.03/O21

Topic: G.09. Drugs of Abuse and Addiction

Support: NSF grant 2051105 (LB, CD)
California Doctoral Incentive Program (MC)
UofM Dunavant Professorship (HS)

Title: Impulsivity and Motivational Deficits in Rats Perinatally Exposed to Delta-9-tetrahydrocannabinol (THC)

Authors: M. S. CARBAJAL[1], L. G. BILLINGS[2], C. M. DIXON[1], ***H. J. K. SABLE**[1];
[1]Psychology, Univ. of Memphis, Memphis, TN; [2]Behavioral Sci., Christian Brothers Univ., Memphis, TN

Abstract: The perception that cannabis (i.e., marijuana) produces little to no harm is widespread, with ~70% of both pregnant and nonpregnant women believing there is slight or no risk associated with cannabis use once or twice a week. In pregnant women, 68% of *medicinal* and 14% of *recreational* cannabis users report self-medicating with cannabis to alleviate morning sickness. This is concerning because perinatal exposure to cannabis has been linked to externalizing behaviors in offspring, including impulsivity. Likewise, in adults, cannabis use has been reported to produce apathy, a lack of initiative, and disinterest in working for appetitive rewards - a state referred to as “amotivational syndrome”. In preclinical research, most studies focus on exposure to the psychoactive constituent of cannabis, delta-9-tetrahydrocannabinol (Δ9-THC). Δ9-THC is lipophilic so it can cross the placental barrier and is secreted in maternal milk, thereby exposing the fetus/neonate during gestation and via lactation. Preclinical data on the effects of perinatal Δ9-THC exposure on impulsive behavior and incentive motivation are extremely limited. Therefore, we orally exposed female nulliparous Wistar rats to a daily dose of 5.0 mg/kg/day Δ9-THC or an equal volume of vehicle placed on a cookie covered in Nutella, beginning 14 days prior to breeding with an unexposed male. Daily dosing of the dam continued until litters were 14 days old. Pups were weaned at 21 days old and one male/female littermate pair allowed to age and tested as adults on both differential reinforcement of high rates (DRH) and differential reinforcement of low rates (DRL) operant tasks. DRH required a minimum number of responses within a set time limit to earn a food reinforcer and was a proxy for incentive motivation. DRL required waiting between lever presses to earn a food reinforcer and was a measure of impulsive action. Rats perinatally exposed to Δ9-THC did not work as hard

(i.e. had fewer lever presses) to earn reinforcers on the DRH task and also had a lower number of reinforced:non-reinforced responses (indicative of impulsivity) on the DRL task. These results validate epidemiological findings reporting perinatal cannabis exposure can increase externalizing behavior, and also suggest perinatal cannabis exposure may promote amotivational syndrome.

Disclosures: M.S. Carbajal: None. **L.G. Billings:** None. **C.M. Dixon:** None. **H.J.K. Sable:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.04/O22

Topic: G.09. Drugs of Abuse and Addiction

Support: Florida Consortium for Medical Marijuana Clinical Outcomes Research
NIH T32 DC000044

Title: Perinatal cannabidiol (CBD) exposure reduces body weight and survival to weaning, and modifies ingestive behavior, object memory, and anxiety- and OCD-like behaviors as an adult

Authors: *M. COMPAGNO[1], A. COX-HOLMES[2], C. MAY[2], F. PACHECO[2], D. A. FADOOL[3];
[1]Mol. Biophysics, Florida State Univ., Tallahassee, FL; [2]Biol. Sci., Florida State Univ., Tallahassee, FL; [3]Prog in Neurosci & Molec Biophys, Florida State Univ., Tallahassee, FL

Abstract: Cannabidiol (CBD) is commonly used to self-treat anxiety, insomnia, or nausea, albeit its only FDA-approved use is for seizures associated with Lennox-Gastaut syndrome. Currently, most CBD products have no guidance for pregnancy. While only 2% of pregnant women admit to CBD use, by uterine and umbilical cord sampling, 26% used CBD or cannabis products (Thompson et al, 2019). We examined consequences of perinatal CBD exposure for postnatal health outcomes and behavior modification as adults. Dams were orally administered 100 mg/kg CBD or vehicle in strawberry jam. CBD was detected in maternal plasma using GC-MS 10-min post consumption (34.2 $\pm$ 1.7 ng/ml), peaked within 30 min (371.0 $\pm$ 34.0 ng/ml), and were below the detection limit by 4 hours (< 10 ng/ml). Pups exposed to CBD had decreased survival, with 37% of CBD-treated pups dying before weaning age (postnatal day 23, P23) while only 8% of jam-treated pups died prior to weaning. Cross-fostering a CBD-treated pup to a drug-free dam mitigated mortality risk. No changes were observed in litter size, maternal body weight or pup birth weight (P0) between CBD and jam-treated animals, however, by postnatal day 10 and 21 (P10, P21), CBD-exposed males weighed significantly less. This was mitigated by cross-fostering to a drug-free dam. At 3 months of age, offspring were metabolically profiled using a comprehensive laboratory animal monitoring system (CLAMS) and challenged via glucose tolerance testing. Perinatal CBD increased meal size and caloric intake for adult male offspring,

with an increase in respiratory exchange ratio greater than 1, indicating an increased use of carbohydrates as fuel (1wANOVA, $p \leq 0.05$). Early postnatal CBD exposure decreased fasting glucose but had no effect on glucose clearance in adult males. Adult offspring were behaviorally phenotyped using the buried marble, light-dark box (LDB), elevated plus maze (EPM), and object memory recognition tests. In utero exposure caused adult offspring to bury more marbles (1wANOVA, $p \leq 0.05$), and females lost this behavior if they were cross-fostered to control dams. In utero exposure decreased time spent in the light compartment of an LDB when females were raised to adults ($p=0.0047$). In utero exposure decreased performance of female mice in the 24-hour object recognition test ($p=0.0123$). Adult female mice spent less time in the closed arms of an EPM if exposed to CBD in utero, and this was unchanged with cross-fostering. In summary, our results support perinatal CBD exposure causes sex-dependent changes in OCD- and anxiety-like behavior, and long-term memory, as well as ingestive behavior, glucose tolerance, and fuel utilization when mice are raised to adults.

Disclosures: M. Compagno: None. **A. Cox-Holmes:** None. **C. May:** None. **F. Pacheco:** None. **D.A. Fadool:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.05/O23

Topic: G.09. Drugs of Abuse and Addiction

Support: Florida Department of Health Ed and Ethel Moore Alzheimer's Disease Research Program Award 21A11

Title: Effects of chronic cannabis smoke exposure on peripheral and brain inflammatory markers and tau pathology in mice

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Abstract: With the rise in cannabis use among older adults, alongside increasing cases of Alzheimer's disease (AD), there is a need to understand how cannabis impacts the aging brain and AD pathology. Aging is associated with an increase in chronic low-grade inflammation, which plays a role in AD pathogenesis. While cannabinoids demonstrate potential in reducing inflammation, protecting against oxidative stress, and lessening plaque burden in AD-like pathology in mouse models, studies often fail to mimic human usage and focus on amyloidosis rather than tauopathy. To address these points, we are evaluating the effects of chronic cannabis smoke exposure on inflammatory markers in young and aged mice, and tau pathology in rTg4510 mutant tau transgenic mice. We exposed young adult (4 months old) and aged (22 months old) C57BL/6J mice (n = 40, half female) to smoke from burning either cannabis (5.9%

THC) or placebo (0% THC) cigarettes daily for 30 days. Serum and brain lysates were analyzed using Quantibody cytokine arrays (RayBiotech). Additionally, rTg4510 tau-overexpressing transgenic mice (n = 23, 4 months old) were exposed to cannabis or placebo smoke daily for 6 weeks. Immunohistochemical analyses for pathological tau using AT8 and AT100 antibodies, as well as Iba1 and GFAP to measure gliosis were conducted. The results revealed that aged mice had significantly higher IL-12p40 serum levels. Aged female mice exposed to cannabis smoke also had higher RANTES serum levels compared to young and aged female mice exposed to placebo smoke, suggesting sex-specific effects of cannabis on aging. Additionally, aged mice had significantly higher levels of P-Selectin, TNF RI, PF4, OPN, Galectin-3, and bFGF in hippocampus and prefrontal cortex compared to young mice (Main effects of Age using 3-way ANOVAs [Sex, Age, Drug]). Male mice experienced more changes in brain inflammatory markers following cannabis smoke exposure compared to female mice. These findings suggest that cannabis smoke affects inflammatory markers differently based on sex, age, and brain region, which could help explain potential effects of cannabis on gliosis and tau pathology progression in rTg4510 mice. Chronic cannabis smoke exposure in rTg4510 mice produced a trend toward decreased GFAP immunostaining in frontal cortex, but not posterior cortex or hippocampus. Further quantification of other immunolabels as well as Western blot analysis of soluble and sarkosyl-insoluble tau levels are ongoing.

Disclosures: E. Gazarov: None. **B. McCracken:** None. **S. Zequeira:** None. **J. Howard:** None. **J.M. Lewis:** None. **J.L. Bizon:** None. **B. Setlow:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.06/O24

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH NIDA Grant #1R01DA049470-02S1

Title: Peripheral and central pharmacological interactions between cannabidiol and oxycodone

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Abstract: We previously showed that co-administering cannabidiol (CBD) potentiates the antinociceptive actions of the opioid oxycodone without potentiating its rewarding effects. Given the apparent contrasting effects of CBD on oxycodone's analgesic and rewarding properties, we sought to determine the pharmacological interactions between CBD and oxycodone in the

plasma and brain, and the impact of co-administration on brain neurochemistry. Sprague Dawley rats (N = 5-6/treatment/sex) were allocated to one of three treatment groups: CBD (10 mg/kg), oxycodone (0.56 mg/kg), or a CBD and oxycodone combination. Animals received daily intraperitoneal administration of drugs for two weeks. Blood samples were collected on days 1, 7, and 14. Brains were extracted after the final drug administration. Punches of the periaqueductal gray, nucleus accumbens, and anterior cingulate cortex were taken from 100 micrometer frozen sections. Plasma and brain tissue were analyzed using mass spectrometry for CBD, oxycodone, their metabolites, and a range of neurochemicals including monoamines and acetylcholine. Our findings suggest that co-administration of CBD with oxycodone potentiated plasma and brain levels of oxycodone, and inhibited oxycodone metabolism. In contrast, CBD metabolism appeared to be slightly accelerated by oxycodone. Rats administered oxycodone alone had the highest levels of brain neurochemical content, particularly serotonin. In contrast, rats co-administered CBD and oxycodone exhibited similar brain neurochemical content as rats administered CBD alone, suggesting that CBD co-administration attenuates the neurochemical effects of oxycodone. The apparent dichotomy of CBD's ability to potentiate oxycodone analgesia without potentiating oxycodone's rewarding effects cannot be explained by potentiation of oxycodone bioavailability. Our findings suggest that CBD co-administration reverses the impact of oxycodone on brain neurochemical activity, thus providing an explanation for why CBD does not affect the rewarding properties of oxycodone. The site at which CBD potentiates the analgesic actions of oxycodone remains to be determined.

Disclosures: A.C. Brice-Tutt: None. **N.P. Murphy:** None. **A.S. Senetra:** None. **T. Serres:** None. **M. Febo:** None. **A.W. Bruijnzeel:** None. **A. Behnood-Rod:** None. **R.M. Caudle:** None. **B. Setlow:** None. **A. Sharma:** None. **J.K. Neubert:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.07/O25

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant 5R01DA039062-08

Title: Effects of THC exposure on sex differences in developmental hippocampal neurogenesis in a rat model

Authors: *C. V. DIONISOS[1], J. W. VANRYZIN[2], M. M. MCCARTHY[3];
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Abstract: Decriminalization of cannabis-containing products and positive perceptions of cannabis use in the United States and other countries have resulted in increased cannabis use among pregnant women to alleviate nausea and pain, but very little is known about the impact on

the developing fetal brain. In rodents, prenatal exposure using Δ9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, upregulates genes associated with neurogenesis in fetal hippocampal development (PMID: 36529297). While various studies looked at effects of THC exposure either prenatally or in adult rodents, few have investigated THC's effects in early postnatal hippocampal development, which corresponds to the third trimester in human pregnancy. There is a well characterized and developmentally restricted sex difference in neurogenesis from birth through the first postnatal week in the rodent hippocampus (PMID: 35255959). On average, males have close to twice as many newborn cells than females during the peak window of postnatal neurogenesis. The sex difference is hormone mediated, as females treated with androgens exhibit male levels of neurogenesis. Here, we investigate whether postnatal THC exposure effects rates of neurogenesis in the developing hippocampus as it does in adult rodents, and whether it does so at similar rates in males and females. THC (5 mg/kg) was administered intraperitoneally once daily from postnatal days 0-3 alongside BrdU (a thymidine analog that marks dividing cells) on postnatal days 1-2. Rat pups were sacrificed on PN4 and histologically analyzed for the density of BrdU+ cells in the upper and lower dentate gyrus of the dorsal hippocampus. We predict that postnatal THC exposure will increase neurogenesis in both sexes, but it is unclear whether the existing sex difference will be exacerbated or abrogated. If neurogenesis is differentially affected by THC in males and females, we will further explore a potential hormonal basis of this sex specific effect in the developing hippocampus, given the knowledge that endocannabinoid tone is mediated by androgens in the developing amygdala. Understanding outcomes of THC exposure on hippocampal development in males and females will inform cannabis use during pregnancy in humans.

Disclosures: C.V. Dionisos: None. **J.W. Vanryzin:** None. **M.M. McCarthy:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.08/O26

Topic: G.09. Drugs of Abuse and Addiction

Support: Quinnipiac University College of Arts and Sciences

Title: Impact of Chronic Oral Cannabidiol Administration on Social Behavior and Protein Expression in Frontal Cortex and Cerebellum of Male and Female Rodents

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Abstract: The endocannabinoid system (ECS) plays a crucial role in modulating different physiological processes, including mood regulation, memory, appetite, and pain sensation. Cannabidiol (CBD) and δ9-tetrahydrocannabinol (THC), derived from the cannabis plant, are

two widely used components for both medicinal and recreational purposes. While the psychoactive component of THC is well studied, the potential therapeutic benefits of CBD are less known. We sought to examine the effects of chronic oral CBD administration in both male and female rats in social behaviors and the alterations in the ECS in the cerebellar lobules IV/V and frontal cortex (medial and orbital) by administering 20mg/kg/day CBD for a total of 28 days. Our findings suggest that there are sex differences in social behavior and changes in the expression of the endocannabinoid receptors CB1 and CB2 at the synaptosomal level. Specifically, the oPFC had a downregulation in both males and females of CB1R compared to mPFC. Additionally, we found alterations in the expression of the degradative enzymes FAAH and MAGL. In summary, this study indicates the complex relationship between the endocannabinoid system, social behavior, distinct brain regions and sex-specific responses to CBD administration, suggesting promising pathways for further research and therapeutic exploration.

Disclosures: S.A. Azerrad: None. **J. Mathews:** None. **A.J. Betz:** None. **H. Jack:** None. **L. Campos:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.09/O27

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH RO1AT011517
Institutional Funds from The University of Arizona

Title: The Terpenes Beta-Caryophyllene and Alpha-Humulene are Aversive in a Conditioned Place Paradigm via Activation of Adenosine A_{2a}Receptors in the Brain

Authors: *A. SCHWARZ[1], A. WELBORN[1], A. PENA[2], J. CARR[1], J. M. STREICHER[1,3]; [1]Med. Pharmacol., Univ. of Arizona, Tucson, AZ; [2]Neurosci. GIDP, The Univ. of Arizona, Tucson, AZ; [3]Comprehensive Center for Pain and Addiction, University of Arizona, Tucson, AZ

Abstract: Terpenes are volatile hydrocarbons found in most plants and contribute to the plant's smell and taste. Our lab has shown that the terpenes β-Caryophyllene (BCP) and α-Humulene (α-hum) relieve neuropathic pain by acting on Adenosine A_{2a} receptors (A_{2a}R) in the spinal cord. We found that BCP and α-hum have opioid-sparing properties for neuropathic pain, a key translational feature. In the presented work, we aimed to **determine if the terpenes BCP and α-hum were rewarding or aversive in a conditioned place (CP) model and the subsequent mechanism of action**. Using CP we determined BCP and α-hum on their own are aversive. To see if the activity of BCP and α-hum at the A2aR contributes to aversion, we implanted cannulas into the left lateral ventricle of mice. We knocked down A_{2a}R expression in the brain with an all-in-one CRISPR-Cas9 construct (A_{2a}R KD; 750ng DNA). The control group was given identical

components but with a non-targeting gRNA (NC). Aversion significantly decreased in $A_{2a}R$ KD mice compared to NC mice for both α-hum and BCP (200mg/kg IP) treatments, suggesting aversion behavior is $A_{2a}R$ mediated. We then assessed the combination of the opioid drug morphine and BCP or α-hum in the CP assay. Mice were treated with morphine (10mg/kg SC) and vehicle, or morphine (10mg/kg SC) and terpene (200mg/kg IP) in an identical paradigm to the isolated terpene CP experiment. BCP and morphine combined showed neither aversion nor reward, suggesting that these drugs could synergize in pain relief while blocking each other's affective side effects.We investigated the potential effects of BCP on the dopaminergic reward system. To do this, we chronically injected mice with morphine (10mg/kg, SC), BCP (200mg/kg IP), or both. We investigated tyrosine hydroxylase (TH) expression within the ventral tegmental area (VTA) to determine if BCP could block morphine's increase in TH, a potential mechanism for its anti-reward effects. Initial results suggested that BCP blocks morphine-induced increases in VTA TH. To further support this hypothesis, we will assess the total and evoked release of dopamine (DA) in *ex vivo* striatal tissue samples using an ELISA kit after identical drug treatment to the TH experiment to assess changes in DA from chronic terpene administration. We anticipate a decrease in dopamine release in terpene-treated mice.Our work suggests the terpene BCP acts via $A_{2a}R$ and when combined with opioid drugs, decreases opioid reward and enhances pain relief. Together, these findings expand our work on the pharmacological properties of terpenes and **suggest that BCP could be an alternate non-opioid, non-cannabinoid therapy for treating neuropathic pain while mitigating opioid reward.**

Disclosures: A. Schwarz: None. **A. Welborn:** None. **A. Pena:** None. **J. Carr:** None. **J.M. Streicher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teleport Pharmaceuticals, LLC, Botanical Results, LLC.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.10/O28

Topic: G.09. Drugs of Abuse and Addiction

Title: Brain-wide effects of cannabinoids, measured by functional ultrasound imaging, show strong correlation with CB1R activation and behavior in awake mice

Authors: *S. DIEBOLT[1], J.-C. MARIANI[2], T. DEFFIEUX[3], M. TANTER[3], A. KLIEWER[4], Z. LENKEI[2];
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Abstract: The emerging therapeutic and recreational use of cannabinoids calls for a better understanding of their brain effects. Using functional ultrasound imaging, we studied the

dynamics of the alterations of brain activation and functional connectivity (FC) patterns, measured through the neurovascular coupling, in a 60-minute period following cannabinoid treatment in awake and behaving C57/BL6J mice. We then correlated these changes with important behavioral and molecular readouts, specifically locomotion, analgesia and CB1 receptor (CB1R) activation, measured by CB1R phosphorylation.
We unveil a robust, dose-dependent and CB1R-specific (i. e. sensitive to AM251 antagonist pre-treatment) fingerprint of brain activation and FC patterns, both after application of THC, the psychoactive component of marijuana, and CP 55,940, a potent CB1R-agonist, but not after application of CBD. Remarkably, these alterations show a strong temporal correlation with changes in locomotion and in analgesia and with CB1R activation.
Our findings show that drug-induced behavioral changes are well correlated with specific brain activation and FC patterns in awake mice. This multimodal imaging approach offers insights into the intricate mechanisms underlying cannabinoid-induced alterations in brain function, enabling future therapeutic avenues targeting the endocannabinoid system.

Disclosures: S. Diebolt: A. Employment/Salary (full or part-time):; ICONEUS. **J. Mariani:** None. **T. Deffieux:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ICONEUS. **M. Tanter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ICONEUS. **A. Kliewer:** None. **Z. Lenkei:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ICONEUS.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.11/O29

Topic: G.09. Drugs of Abuse and Addiction

Support: FLINSTUD-Forskerlinjen/Studentstipend

Title: Effect of tetrahydrocannabinol on cortical synapse development in adolescent mice

Authors: *K. M. TOHVER[1], T. GÜNTHER[1], I. JAROS[1], M. N. MOEN[1], T. EID[3], S. HUSSAIN[1,2], S. DAVANGER[1];
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Abstract: An increase in legalization and acceptance of cannabis use has resulted in an increased use of the drug by adolescents, while many of its developmental effects and mechanisms on the brain remain unknown. Adolescence is a crucial period for brain maturation through synaptic plasticity and pruning, processes which cannabis may disrupt. Particularly of interest is the Anterior Cingulate Cortex (ACC) which is associated with complex cognitive functions,

including emotional and social memory, fear, and social decision-making. Understanding the molecular and synaptic effects of cannabis on the ACC in adolescence is crucial for comprehending its impact on cognitive and emotional development. Our study aimed to determine possible synaptic changes in adolescent (2-3 month old) female mouse ACC after moderate (3μg/g of body weight) Δ-9-tetrahydrocannabinol (THC) treatment via abdominal injection every third day for a total of six injections, simulating moderate recreational use. Through quantitative Western Blotting of ACC and hippocampal homogenates, we screened a variety of synaptic proteins including glutamate receptors, BDNF, Arc, synaptophysin, syntaxin 1, synaptotagmin 1 and PSD-95. Synaptotagmin 1 (SYT1) alone showed a significant, 55.5% decrease in the ACC ($P<0.04$) and 82.1% decrease in the hippocampus ($P<0.01$) in the THC treated animals compared to the controls. In order to investigate changes in SYT1 at the subsynaptic level, we conducted quantitative post-embedding immunogold electron microscopy. Additionally, we assessed the behavioral effects of THC with three-chamber sociability test, and analyzed synaptic density and morphology in the ACC using Golgi staining. The results from these experiments will be presented at the conference. Changes in SYT1 may have a negative impact on synchronous pre-synaptic vesicle release, and possibly on pre- and postsynaptic glutamate receptor trafficking. Alongside potential changes in synaptic density and morphology in the ACC, these changes may provide the basis for altered social behavior observed in cannabis users.

Disclosures: K.M. Tohver: None. **T. Günther:** None. **I. Jaros:** None. **M.N. Moen:** None. **T. Eid:** None. **S. Hussain:** None. **S. Davanger:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.12/O30

Topic: G.09. Drugs of Abuse and Addiction

Title: Prenatal Stress and THC exposure impact maternal and adolescent behaviors

Authors: *J. OLUSAKIN[1], M. DEWAN[2], M. LOBO[3];
[1]Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Med., Univ. of Maryland Sch. of Med., Germantown, MD; [3]Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Cannabis is the most used illicit substance worldwide. The commonly cited reasons for continued cannabis use in chronic users is to cope with elevated stress (and/or) anxiety levels, pain and nausea. Pregnant women will often use cannabis to control nausea or stress/anxiety, and the effectiveness of cannabis in controlling these symptoms is likely due to the regulation of dopaminergic signaling in the reward-related brain areas. The main psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), can readily cross the placenta during gestation, and is also secreted in the maternal milk during lactation. In addition, both clinical and preclinical studies have shown that chronic exposure to cannabis during gestation and lactation

can induce behavioral teratogenic consequences. Little is known about the compound effects of prenatal exposure to stress and cannabis on long-term behaviors and cognition in adolescent offspring. In this study, pregnant dams underwent 10 days of chronic witness defeat stress (CWDS) from embryonic day 0 (E0) and concurrent administration of subcutaneous i.p injections of 2mg/kg THC from E0 till birth. Following the 10 days of CWDS, we tested dams for anxiety-like behaviors - open field (OFT) and elevated plus maze (EPM), and social interaction (SI). At postnatal day 35 (P35), in addition to testing adolescent offsprings exposed to prenatal stress and THC on SI, OFT, EPM and splash tests, we further tested them on effort-related choice task using the Y-maze barrier test, a read-out for motivation. Our downstream behavior analysis in the dams reveal a significant interaction effect of THC and stress in the social interaction test and open field test suggesting that compound exposures to stress and THC exacerbated anxiety-like behaviors. In the adolescent mice, we observed significant interaction effects of Prenatal THC and stress in the splash test suggesting a decrease in motivation to groom. Further, we observed sex specific differences in anxiety-like behaviors. Particularly, prenatal THC and stress exposed male adolescent mice showed decreased time spent exploring the open arm and center of the EPM and OFT respectively suggesting that compound exposures to prenatal THC and stress exacerbated anxiety-like behaviors. While we did not observe any interaction effects of prenatal THC and stress in the effort related test for motivation, we did find main effects of THC and stress in females and just main effect of stress in males in the 10cm barrier testing. Our on-going investigating aims at identifying possible gene substrates within the prefrontal cortex and nucleus accumbens driving our observed negative affects.

Disclosures: J. Olusakin: None. **M. Dewan:** None. **M. Lobo:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.13/O31

Topic: G.09. Drugs of Abuse and Addiction

Support: WSU University Research Grant

Title: A Matter of Risk: Examining Rates of Use and Risk Perception of Cannabis and Cannabidiol Use in Pregnant Detroit-Area Women

Authors: *E. R. CRISAN[1], N. SHAKOURI[3], J. CORKINS[3], H. MARUSAK[2];
[2]Psychiatry and Behavioral Neurosciences, [1]Wayne State Univ. Sch. of Med., Detroit, MI;
[3]Wayne State Univ., Detroit, MI

Abstract: Background: Cannabis use has grown significantly in the United States alongside increased legalization and commercialization, and it remains the most widely used illicit drug in the U.S. Recent studies indicate that cannabis use during pregnancy is common, with 6% of women in national surveys reporting use and up to 20% in younger populations. However,

emerging data link prenatal cannabis exposure to adverse outcomes in children, including lower birth weight and attentional, social, and behavioral problems. Little is known, however, about cannabidiol (CBD) products, which are widely accessible and legal nationwide. The present study was designed to examine the prevalence of CBD use or co-use with cannabis or Δ-9 tetrahydrocannabinol (THC)-containing products, in pregnant Detroit-area women. We also examined perceived risk of using CBD and cannabis during pregnancy, compared to other commonly used substances.**Methods:** Here, we report on preliminary data from an ongoing survey study to assess rates and perceptions of use of cannabis, CBD, and other substances in pregnant Detroit-area women, ages 18+. To-date, the sample includes 20 women ($M \pm SD$ = 27.8±5.3 years, 70% White, 80% singleton pregnancies). Descriptive statistics were used to evaluate use and perceptions of risk. Chi-square or *t*-tests were used to compare use patterns and average risk scores between substances, respectively. **Results:** Thirty percent of women endorsed cannabis use during pregnancy, and only fifteen percent endorsed CBD use. Across the sample, ratings of perceived risk significantly differed between cannabis and CBD, with a large portion rating cannabis as "OK to use" during pregnancy but believing that women should "Reduce use" of CBD, χ^2 (4) = 19.4, $p < 0.001$. However, average perceived risk did not differ between substances, $p > 0.05$. Caffeine and alcohol were the only other drugs reported prior to/during pregnancy, with 60% and 30% endorsing prenatal use, respectively. Both substances had significant differences in risk perception compared to CBD ($p < 0.05$) with CBD being rated as higher risk than alcohol; ratings of CBD and caffeine were split.**Conclusions:** Preliminary results suggest that 30% of pregnant Detroit-area women use cannabis during pregnancy, which is much higher than national averages. Surprisingly, CBD use was less common than cannabis, despite its legal status as a supplement. In addition, a larger portion of pregnant women reported that cannabis is safe to use but CBD is not. It is unclear what is driving the difference in usage and risk perception of cannabis compared to CBD. More research needs to be done to characterize cannabinoid usage in pregnant women.

Disclosures: E.R. Crisan: None. **N. Shakouri:** None. **J. Corkins:** None. **H. Marusak:** None.

Poster

PSTR361: Exogenous Cannabinoids, Inflammation, Development and Risk Factors

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR361.14/O32

Topic: G.09. Drugs of Abuse and Addiction

Support: California Doctoral Incentive Program (MC)
UofM Dunavant Professorship (HS)

Title: Perinatal Exposure to Delta-9-tetrahydrocannabinol (THC) Alters Dopamine Functioning in Wistar Rats

Authors: *M. S. CARBAJAL, R. C. CRENSHAW, H. J. K. SABLE, D. B. LESTER; Psychology, Univ. of Memphis, Memphis, TN

Abstract: The number of people who consume cannabis (i.e., marijuana) is steadily increasing in the US general population and among pregnant women. In a 2019 study in Colorado, 23% of pregnant patients tested positive for delta-9-tetrahydrocannabinol (THC; the psychoactive constituent of cannabis) at the time of delivery. Many users believe cannabis is a safe option for alleviating symptoms associated with pregnancy, such as nausea, anxiety, and insomnia. However, there is clinical evidence linking perinatal exposure to cannabis and externalizing behavior in offspring. Similarly, we have shown that rats exposed to THC during gestation and lactation displayed motivational deficits and increased impulsivity as adults. Given the role of dopamine in mediating behaviors related to motivation and impulsivity, the current study aimed to determine the effects of perinatal THC exposure on dopamine functioning in the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC). We orally exposed nulliparous Wistar females to a daily dose of 5.0 mg/kg/day THC or an equal volume of vehicle placed on a cookie covered in Nutella, beginning 14 days prior to breeding with an unexposed male. Daily dosing of the dam continued until litters were 14 days old. Pups were weaned at 21 days old and one male/female littermate pair allowed to age and tested as adults using *in vivo* fixed potential amperometry for measures of stimulation-evoked phasic dopamine release while anesthetized. During NAc dopamine recordings, rats received an injection of cocaine (10 mg/kg, ip) as a challenge to their reward system. In male rats, perinatal THC exposure did not alter baseline dopamine release in the NAc or mPFC; however, perinatal THC exposure did result in an attenuated dopaminergic response to cocaine, with cocaine-induced changes in NAc dopamine release being significantly greater in control rats (229%) compared to THC-exposed rats (156%). These results complement behavioral findings that perinatal THC exposure decreases interest in working for reinforcers, providing neurochemical support for perinatal THC exposure promoting amotivational states. The dopaminergic effects of perinatal THC exposure in female rats are being analyzed.

Disclosures: M.S. Carbajal: None. **R.C. Crenshaw:** None. **H.J.K. Sable:** None. **D.B. Lester:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR362.01/O33

Topic: G.09. Drugs of Abuse and Addiction

Support: NCCIH R01AT011524

Title: Cannabidiol inhibits c-Jun N-terminal Kinase (JNK) to block JNK-dependent reactive oxygen species production

Authors: *K. QIU[1], S. E. MAR[2], A. ENGLISH[1], S. S. SCHATTAUER[1], B. B. LAND[2]; [2]Pharmacol., [1]Univ. of Washington, Seattle, WA

Abstract: Cannabidiol (CBD), a non-psychoactive cannabinoid compound, has been reported to have analgetic properties and may interact with opioids to better control pain. Previous work from our group has established connections between morphine tolerance and Reactive Oxygen Species (ROS) production through c-Jun N-terminal Kinase (JNK)-mediated Peroxiredoxin 6 (PRDX6) activation. Excess ROS production promotes desensitization of opioid receptors, which in turn leads to opioid tolerance. However, if and how CBD intersects with the JNK/PRDX6 pathway to modulate ROS production is unknown. We investigated the connections between CBD administration and JNK activity at the cellular and biochemical levels. We used molecular docking simulations to show that CBD has a favorable docking pose with JNK at the site where other JNK inhibitors are predicted to bind. In vitro kinase assays for JNK confirmed that CBD inhibited JNK phosphorylation in a dose-dependent manner. Next, we performed live cell imaging and found that CBD decreases ROS production as a function of morphine administration. Because JNK signaling is associated with pain and ROS, we hypothesized that CBD decreases ROS production during pain states, consistent with its anti-inflammatory profile. Wild-type HEK 293 cells were transfected with oROS, a genetically encoded sensor that fluoresces proportionally to ROS production. Cells expressing oROS were treated with buffer (control) and/or CBD before administration of Tumor Necrosis Factor alpha (TNFα), a known activator for JNK released during pain states. ROS production was quantified and compared between groups with and without CBD pretreatment to determine CBD's activity on inhibiting JNK-mediated pro-inflammatory pathways. Compared to the control group, cells pre-treated with CBD showed significantly less ROS production. To determine the interaction of CBD and JNK on a biochemical level, western blot analyses were performed using a preclinical model of chronic pain. Mice were given either partial sciatic nerve ligation surgery or sham surgery and underwent voluntary gelatin administration of either control or CBD (20 mg/mL) for 7 days post-surgery. Mice were sacrificed on day 7, and spinal cord tissue was stained for pJNK and pc-Jun, the protein phosphorylated downstream of JNK. We predict that pSNL surgery will cause elevated phosphorylated JNK levels, and treatment of CBD through gelatin administration will inhibit this elevation. These data are consistent with the hypothesis that CBD directly inhibits JNK activity during pain states and morphine treatment, providing a mechanistic model for how CBD modulates both pain and opioid function.

Disclosures: K. Qiu: None. **S.E. Mar:** None. **A. English:** None. **S.S. Schattauer:** None. **B.B. Land:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

Location: MCP Hall A

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Topic: G.09. Drugs of Abuse and Addiction

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Title: Deep brain stimulation of the ventral tegmental area attenuates fentanyl-evoked serotonin release in the rat nucleus accumbens: Potential mechanisms of action

Authors: *J. M. ROJAS CABRERA[1,2,3], B. A. HANNA[4], S. VETTLESON-TRUTZA[1,5], K. M. SCHEITLER[1,3,5], C. D. BLAHA[1,3], Y. OH[1,3,6,7], K. H. LEE[1,3,7], H. SHIN[1,3,6];
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Abstract: Fentanyl is a potent synthetic opioid and a major contributor to the rise in drug overdoses in the USA. Although serotonin (5-HT) in the nucleus accumbens core (NAcc) has been implicated in synthetic opioid addiction, studies on serotonergic responses to fentanyl are few compared to those of dopamine. In addition, current evidence supports the use of ventral tegmental area (VTA) deep brain stimulation (DBS) therapy for treatment-refractory drug addiction. Here, we examined the effects of fentanyl on basal extracellular levels of 5-HT in the NAcc and on respiratory depression including the ability of VTA high-frequency stimulation (HFS, DBS-like) to ameliorate these fentanyl-induced neurochemical and respiratory effects. A carbon fiber microelectrode was placed in the NAcc and a concentric stimulating electrode was placed in the VTA of urethane (1.5 g/kg, i.p.) anesthetized rats. Basal NAc 5-HT levels were monitored with N-shaped multiple cyclic square wave voltammetry (N-MCSWV). In Aim 1, basal recordings for a 1hr period were followed by a bolus of fentanyl (50 μg/kg, i.v., 10s injection). In Aim 2, basal recordings for 1hr were followed by 1.5hrs of continuous HFS of the VTA (130Hz, 0.2ms biphasic PW, 0.2mA). After 1hr of HFS, fentanyl was injected, and basal 5-HT monitoring continued for the remaining 30min of HFS. Respiration rate was captured throughout the duration of the experiment in both aims with a pressure-sensing device (RespiRat). Fentanyl evoked a rapid increase in basal 5-HT within the NAcc by 869.2% from baseline. In addition, respirations per minute (rpm) began declining immediately after the bolus injection (110.7 rpm pre-drug, 43.2 rpm 5min post-drug). HFS of the VTA reduced basal 5-HT levels by 54.5% within the NAcc compared to baseline. Basal 5-HT levels increased 255.9% from baseline with fentanyl during HFS of the VTA. Lastly, fentanyl-induced respiratory depression was ameliorated with continuous VTA stimulation (109.2 rpm pre-drug, 45.6 rpm 5min post-drug, 88.6 rpm 15min post-drug). Here, we show that HFS ameliorates the effects of fentanyl on both increases in basal 5-HT levels and respiratory depression. Further studies will determine if the effects of VTA HFS on fentanyl are due to depolarization block of serotonergic axonal transmission and/or depletion of vesicular stores of 5-HT in serotonergic terminals in the NAcc. Overall, these results support the possibility of using neuromodulation technology for treatment of opioid addiction and potentially other drugs of abuse such as psychostimulants.

Disclosures: J.M. Rojas Cabrera: None. **B.A. Hanna:** None. **S. Vettleson-Trutza:** None. **K.M. Scheitler:** None. **C.D. Blaha:** None. **Y. Oh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NaviNetics, Inc. **K.H. Lee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NaviNetics, Inc.. **H. Shin:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR362.03/O35

Topic: G.09. Drugs of Abuse and Addiction

Support: F99NS129176

Title: Opioid inhibition of neurons in the anterior paraventricular nucleus of the thalamus

Authors: *O. KOITA[1], J. T. WILLIAMS[2];
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Abstract: Neurons in the rat anterior PVT (aPVT) integrate visceral and emotional signals to bias behavior toward aversive or defensive states and are sensitive to the inhibitory actions of opioids. How the heterogeneous population of neurons in this area are regulated by mu-opioid receptor (MOR) activation acutely and following chronic opioid treatment remains to be determined. This study examines neurons in the aPVT from male and female rats that project to the amygdala, nucleus accumbens, and prefrontal cortex using patch clamp electrophysiology. Application of [Met]5enkephalin activated potassium conductance in more than 90% of neurons studied that projected to each area. The opioid-induced current in amygdala-projecting neurons was larger than those projecting to the nucleus accumbens and medial prefrontal cortex. Application of a saturating concentration of ME (30 µM, 10 min) resulted in a peak current that declined during the application (desensitization) in recordings from neurons that projected to each brain area. Inhibition of the G Protein Receptor Kinase (GRK2/3) with compound101 blocked desensitization indicating a phosphorylation-dependent process. In animals treated chronically with morphine, there was a decrease in sensitivity to morphine in the amygdala and nucleus accumbens but little or no tolerance in mPFC projecting neurons. During acute withdrawal, the percentage of neurons that fired spontaneously increased although there was no change in the frequency of action potentials. Further, we show that during naloxone-precipitated withdrawal and the application of a depolarizing step, the number of action potentials was increased in neurons that projected to the NAc but little or no change in the neurons projecting to the mPFC or amygdala. Taken together the results indicate that there are cell selective adaptive mechanisms that alter the activity of aPVT neurons following chronic morphine treatment. Receptor-dependent tolerance would contribute to dose escalation, while the increased excitability would contribute to signs of withdrawal.

Disclosures: O. Koita: None. **J.T. Williams:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA IRP

Title: Deletion of mu opioid receptors from astrocytes fails to alter opioid reward and analgesia

Authors: *E. LINZ[1], G.-H. BI[1], O. SOLER-CEDENO[1], H. ALTON[2], Z. XI[3];
[1]Natl. Inst. on Drug Abuse, Baltimore, MD; [2]NIH, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD; [3]Intramural Res. Program, Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Much of the research conducted on opioid receptors in recent decades has focused on their expression and function within neurons, particularly within inhibitory GABAergic neurons in the brain. However, recent studies indicate that mu opioid receptors (MOR), encoded by the *Oprm1* gene, are also present in astrocytes and microglial cells. While the involvement of GABAergic MOR in opioid reward and analgesia is well-documented, the functional significance of astrocytic MOR in opioid action remains largely unexplored. This study aimed to investigate whether astrocytic MOR play a role in opioid reward and analgesia. Using Cre-LoxP technology (Oprm1-flox × GFAP-CreER), we selectively deleted the *Oprm1* gene in astrocytes while maintaining its expression in other cell types. Tamoxifen (100 mg/kg, i.p., for 5 consecutive days) was administered to activate Cre expression by binding to the human estrogen receptor (ER) fusion protein, leading to excision of the *Oprm1* gene sequence in adult mice. Behavioral responses to opioids were then compared between Oprm1-knockout (GFAP-Oprm1-KO) mice and wildtype littermates (Oprm1-flox) 4-5 weeks after the final tamoxifen injection. A variety of behavioral assays were conducted, including intravenous heroin self-administration, oxycodone-induced conditioned place preference, open field locomotion, hot-plate analgesia, and tail-flick analgesia assays. Interestingly, no significant differences were observed between GFAP-Oprm1-KO mice and Oprm1-flox control mice in any of the behavioral tests. These findings suggest that MOR on astrocytic cells may not play a significant role in the behavioral responses to opioids, including opioid reward and analgesia.

Disclosures: E. Linz: None. **G. Bi:** None. **O. Soler-Cedeno:** None. **H. Alton:** None. **Z. Xi:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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NIH Grant DA053443

Title: Pivotal role of orexin signaling in the posterior paraventricular nucleus of the thalamus during the stress-induced reinstatement of oxycodone-seeking behavior

Authors: *J. ILLENBERGER, F. J. FLORES-RAMIREZ, **R. MARTIN-FARDON**;
The Scripps Res. Inst., La Jolla, CA

Abstract: AIM: The orexin (OX) system has received increasing interest as a potential target for treating substance use disorder. Orexin transmission in the posterior paraventricular nucleus of the thalamus (pPVT), an area that is activated by highly salient stimuli that are both reinforcing and aversive, mediates cue- and stress-induced reinstatement of reward-seeking behavior. Oral administration of suvorexant (SUV), a dual OX receptor (OXR) antagonist (DORA), selectively reduced conditioned reinstatement of oxycodone-seeking behavior and stress-induced reinstatement of alcohol-seeking behavior in dependent rats. This study tested whether OXR blockade in the pPVT with SUV reduces oxycodone or sweetened condensed milk (SCM) seeking elicited by conditioned cues or stress. **METHODS:** Male Wistar rats were trained to self-administer oxycodone (0.15 mg/kg, i.v., 8 h/day) or SCM (0.1 ml, 2:1 dilution [v/v], 30 min/day). After extinction, the ability of intra-pPVT SUV (15 µg/0.5 µl) to prevent reinstatement of oxycodone or SCM seeking elicited by conditioned cues or footshock stress was tested. **RESULTS:** The rats acquired oxycodone and SCM self-administration, and oxycodone intake correlated with signs of physical opioid withdrawal, confirming dependence. Following extinction, the presentation of conditioned cues or footshock stress elicited reinstatement of oxycodone- and SCM-seeking behavior. Intra-pPVT SUV blocked footshock stress-induced reinstatement of oxycodone seeking but not conditioned reinstatement of oxycodone or SCM seeking or stress-induced reinstatement of SCM seeking. **CONCLUSIONS:** The results indicate that OXR signaling in the pPVT is critical for stress-induced reinstatement of oxycodone seeking, further corroborating OXRs as treatment targets for opioid use disorder. This work was supported by The National Institute on Alcohol Abuse and Alcoholism (grant no. AA006420, AA026999, AA028549, and T32 AA007456) and The National Institute on Drug Abuse (grant no. DA053443).

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Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR362.06/P1

Topic: G.09. Drugs of Abuse and Addiction

Support: Arizona State University Startup Funds

Title: The effect of spontaneous withdrawal from oxycodone on anhedonia, social behavior, and gene expression

Authors: *O. LAW[1], J. C. GEWIRTZ[2], J. L. VERPEUT[2];
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Abstract: In the last two decades, there has been a steep rise in prescription opioid use, and individuals taking prescription opioids for an extended time are at an especially high risk for developing opioid use disorder. Importantly, cessation of opioids can lead to both somatic and affective withdrawal symptoms which may precipitate relapse. As such, additional research into opioid withdrawal is needed to better understand the behavioral and neurobiological mechanisms of addiction. The aim of the current study was to examine the effect of spontaneous withdrawal from oxycodone in male and female C57BL/6J mice following a repeated injection regimen (5mg/kg/day or 10 mg/kg/day oxycodone for 10 days) on behavior, neuronal activity, and RNA expression. Oxycodone physiological efficacy was confirmed using the hotplate assay which measures thermal nociception. Mice were placed on a 50-55° C hot plate and measured for latency to lick their forepaws. Those injected with an acute dose of oxycodone showed an increased latency to lick at 15 minutes post-injection relative to controls. We hypothesized that withdrawal from oxycodone would lead to withdrawal-induced anhedonia (WIA), characterized by a decrease in sucrose preference and social behavior in mice. First, animals were presented with a two-bottle choice test between sucrose and water prior to drug exposure and during withdrawal. There was no evidence of WIA using the sucrose preference task at a 2% or 10% concentration of sucrose or at a 15% concentration of sweetened condensed milk. Group social behavior was assessed in an elevated open field for 30 minutes before drug exposure and during withdrawal. Results were analyzed using the machine learning algorithm SLEAP (Social LEAP Estimates Animal Poses). Oxycodone-withdrawn mice demonstrated decreased locomotion ($p = 0.003$), increased time spent ($p = 0.009$) in the corners, and decreased time spent around the hut ($p = 0.05$) relative to controls. We are currently examining levels of neuronal activation in the prefrontal cortex and anterior cingulate cortex using the immediate early gene, c-Fos. In addition, we will use quantitative polymerase chain reaction (qPCR) to examine levels of RNA expression. By using a combinatory study examining individual behavior, social behavior, and spatial and quantitative patterns of gene expression, we can create a comprehensive withdrawal profile following repeated oxycodone use which may have implications in the treatment of opioid addiction.

Disclosures: O. Law: None. **J.C. Gewirtz:** None. **J.L. Verpeut:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Program #/Poster #: PSTR362.07/P2

Topic: G.09. Drugs of Abuse and Addiction

Support: 5R01DA038168-10

Title: Orexin and dynorphin as the neuropeptidergic modulators of the paraventricular thalamic nucleus (PVT) neuronal activity

Authors: *M. TRZECIAK[1], H. P. STEVENSON[1], H. S. PLATTER[1], G. D. STUBER[2]; [2]Anesthesiol. and Pain Med., [1]Univ. of Washington, Seattle, WA

Abstract: Orexin and dynorphin as the neuropeptidergic modulators of the paraventricular thalamic nucleus (PVT) neuronal activity
Authors: Marta Trzeciak[1], Hannah P. Stevenson[2], Garret D. Stuber[1,21]Department of Pharmacology, University of Washington, [2]Center for the Neurobiology of Addiction, Pain, and Emotion, Department of Anesthesiology and Pain Medicine
Abstract: The paraventricular thalamic nucleus (PVT), a crucial yet often overlooked nucleus of the dorsal midline thalamus, stands as a pivotal integrator within the brain's circuitry, particularly influencing motivated and reward-driven behaviors. Notably, the lateral hypothalamus densely projects to both the anterior and posterior regions of the PVT, serving as a significant source of orexinergic and dynorphinergic inputs. While prior research indicates dynorphin's role in aversive states and orexin's in promoting arousal, the specific modulatory effects of these neuropeptides on PVT neuronal activity and downstream regions remain elusive. In this study, employing hybridization *in situ* (HCR), we identified differences in distribution of postsynaptic receptors mediating the effects of orexin and dynorphin. Our findings revealed significant differences in the expression of kappa opioid receptor 1 (*Oprk1*) and orexin receptor 1 (*Hcrtr1*) across the anterior-posterior axis of the PVT. To address acute effects on the PVT neurons calcium activity we used two-photon calcium imaging in brain slices acquired across anterior-posterior axis. Our results demonstrate that bath application of orexin or dynorphin respectively increased or decreased calcium activity, accompanied by synaptic activity-dependent oscillations. To elucidate the circuitry-related effects, we mapped the prodynorphinergic and orexinergic projections to the PVT using retroviruses. Our data highlighted the lateral hypothalamus as a crucial peptidergic source, further investigated through electrophysiological studies and fiber photometry using AAV5-DIO-ChR2-EYFP. In the future, we aim to disentangle the intertwined signaling mediated by orexin and dynorphin and provide better understanding of behaviors mediated and modulated within PVT.
Keywords: PVT, neuropeptides, dynorphin, orexin

Disclosures: M. Trzeciak: None. **H.P. Stevenson:** None. **H.S. Platter:** None. **G.D. Stuber:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

Location: MCP Hall A

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Program #/Poster #: PSTR362.08/P3

Topic: G.09. Drugs of Abuse and Addiction

Title: Small Molecule Therapeutics for Opioid Addiction

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Abstract: Opioids alter gene expression via modifications in DNA histone methylation patterns, and these changes may underlie the addictive nature of opioid abuse. Mechanism(s) involved in opioid-induced epigenetic changes include inhibition and degradation of the EAAT3 transporter required for uptake of the amino acid, L-cysteine, into neurons. Once inside cells, L-cysteine is converted to the antioxidant glutathione (GSH), which maintains redox homeostasis in cells. As a consequence of opioid exposure, neurons become deficient in cysteine and GSH, which results in an inability of neurons to maintain proper redox control. Previous research has shown that impaired redox control is involved in the expression of opioid withdrawal, thus drug therapies which prevent redox dysregulation and facilitate redox homeostasis may be of benefit in the treatment of opioid use disorders. Redox control and DNA/histone methylation reactions are linked to methionine metabolism. It has been shown previously that D-cysteine ethyl ester (D-CYSee) and betaine, a methyl donor, lowered cellular stress and restored epigenetic potential. The goal of the present study was to evaluate the effects of D-CYSee and betaine on redox homeostasis and DNA methylation levels during morphine (MOR) treatment. Neuroblastoma cells were treated for 24-hours with MOR (100 nM) in the absence and presence of betaine or D-CYSee. GSH levels and mitochondrial membrane potential were then recorded using GSH Colorimetric Assay and JC-1 staining. Data was evaluated by one-way ANOVA with Bonferroni corrections or Student's two-tailed t-test depending on the data. A $p < 0.05$ was considered significant. Co-treatment with Betaine or D-CYSee prevented morphine-induced depletion of GSH levels and stimulated a MOR dependent increase in GSH that exceeded intervention free control ($n = 4$, $p < 0.05$). Co-treatment with D-CYSee or betaine also prevented MOR induced changes in mitochondrial membrane potential and increased global DNA methylation ($p < 0.05$, $n = 3$). In conclusion, D-CYSee and betaine reduces cellular stress and prevents abnormal methylation patterns observed in cultured neurons. This shows that D-CYSee and betaine may be a potential treatment for opioid addiction.

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Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Program #/Poster #: PSTR362.09/P4

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH R21-DA057418
The McManus Foundation

Title: Characterization of ventral tegmental area neuromedin-s expressing neurons

Authors: *K. MCGRATH[1], C. M. RIVERA QUILES[1], O. DODSON[1], M. S. MAZEI-ROBISON[2];
[1]Neurosci., [2]Michigan State Univ., East Lansing, MI

Abstract: Despite the presence of treatments for opioid use disorder (OUD), opioids remain the leading cause of overdose deaths in the U.S. By studying neurobiological effects of chronic opioid use, we hope to better understand OUD, which could lead to better treatments. The ventral tegmental area (VTA) of the brain is a critical region for motivated behaviors. Specifically, dysfunction of dopaminergic neurons (DA) of the VTA can contribute to addictive behavior. We have found that neuromedin S (NMS) gene expression is increased by chronic morphine in VTA DA neurons. Given our novel finding of NMS expression in the VTA, we are interested in characterizing NMS-expressing neurons in the VTA, including their expression patterns and projections. To investigate this, we injected Cre-dependent excitatory DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) into the VTA of NMS-Cre mice and administered clozapine-n-oxide (CNO) to activate VTA-NMS neurons. After perfusion and brain slicing, we performed immunohistochemistry on VTA coronal sections to assess mCherry and tyrosine hydroxylase expression (TH) to identify NMS cells expressing the DREADD and dopaminergic neurons, respectively. We found that in naïve mice less than 5% of dopamine neurons express NMS. However, in mice that underwent morphine locomotor or morphine conditioned place preference (CPP) experiments to determine behavioral differences induced by VTA-NMS neuron activation, the percentage of VTA-NMS cells increased. We are also using a retrograde viral tracer approach to identify projection targets of VTA-NMS cells. Our initial studies indicate that VTA-NMS neurons project to the nucleus accumbens and lateral hypothalamus, but not the prefrontal cortex. Taken together, these studies suggest that VTA-NMS neurons represent a subset of DA neurons, and that VTA-NMS circuitry may represent a novel target for intervention for OUD.

Disclosures: K. McGrath: None. **C.M. Rivera Quiles:** None. **O. Dodson:** None. **M.S. Mazei-Robison:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR362.10/P5

Topic: G.09. Drugs of Abuse and Addiction

Title: Single-cell whole-brain imaging reveals differences in functional organization of pain, anxiety and sensory regions following mu and kappa opioid receptor agonism

Authors: *S. BONNET-ZAHEDI[1,2], L. L. CARRETTE[1], S. SOTNIKOV[1], B. RYABOV[1], A. R. MARTINEZ[1], B. BOOMHOWER[1], M. PAVLICH[1], A. COLLAZO[3], O. GEORGE[1]; [1]Psychiatry, Univ. of California San Diego, San Diego, CA; [2]Inst. des Neurosciences, Aix-Marseille Univ., Marseille, France; [3]Caltech, Pasadena, CA

Abstract: Opioids, specifically mu-opioid receptor (MOR) agonists, are pivotal in pain research because of their analgesic efficacy but have a high potential for abuse due to their addictive properties. Conversely, kappa opioid receptor (KOR) activation can have pain-relieving, pain-producing, and dysphoric effects, serving as a deterrent against misuse. This study aims to understand how the brain-wide functional networks are differently affected by MOR and KOR agonists, providing insight into their impact on pain, reward, anxiety and sensory-related regions. Single-cell whole-brain imaging in mice (*n*=32, 16 male and 16 female) mapped neuronal activity induced by the MOR agonist Heroin (20 mg/kg) and KOR agonist Salvinorin A (2 mg/kg). Their effect on analgesia, locomotion, and anxiety-like behavior were assessed. Brains were perfused 90 min after injection, immunolabeled for Fos, and imaged via light-sheet microscopy. The ClearMap pipeline automatically detected and counted cells in the microscopy images. As previously reported, both Heroin and Salvinorin A treatment induced analgesia, with Heroin significantly increasing mobility and Salvinorin A reducing it. These results aligned with an overall increase in whole-brain Fos reactivity with Heroin compared to Salvinorin A, particularly driven by heroin-induced reactivity increase in the isocortex and striatum and Salvinorin A-induced reactivity decrease in the isocortex and hypothalamus. The reactivity changes resulted in differential effects on the derived functional connectivity. Heroin treatment caused segregation between the forebrain from the midbrain and hindbrain, clustering of emotion, anxiety, and sensory-related regions into a major module. Whereas Salvinorin A treatment caused a strong disconnection of the isocortex and moderate segregation of the hindbrain and hypothalamus from the other regions, grouping together pain-related regions in one module and most sensory regions in another. The study identified, using single-cell whole-brain imaging, the divergent impact of MOR and KOR agonism on the brain state, underlying the behavioral effects. This method gives crucial insights into pain-relief drugs' effects on brain reactivity and connectomic changes. These new insights could also assist in the development of non-addictive analgesics.

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Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Program #/Poster #: PSTR362.11/P6

Topic: G.09. Drugs of Abuse and Addiction

Title: Xylazine induces dopamine release in the nucleus accumbens and augments the effects of fentanyl

Authors: *J. R. TRINKO, E. FOSCUE, **E. KONG**, A. BASU, A. CORSTENS, S. L. THOMPSON, A. P. KAYE, J. TAYLOR, R. J. DILEONE;
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Abstract: Opioid-related drug overdoses have dramatically increased in the United States. The mixture of fentanyl and xylazine, more commonly known as “Tranq-Dope” has become increasingly prevalent in recent years with 23% of seized fentanyl powder containing traces of xylazine, an α2-adrenergic receptor agonist and established veterinary sedative. Emergency medical treatments such as naltrexone have little to no effect on xylazine’s pharmacological impact since they are specifically tailored towards opioids. The incorporation with fentanyl makes critical that we understand their effects on the brain and their pharmacological interplay. This study investigated the effects of xylazine, fentanyl, and their interaction, focusing on dopamine release within the nucleus accumbens (NAc), a key brain region involved in drug reward and locomotor activity. We utilized fiber photometry to monitor real-time $GRAB_{DA}2M$ fluorescence as an indicator of synaptic dopamine in mice, as well as DeepLabCut, an AI-based toolbox to assess locomotor activity simultaneously with fiber photometry measures. A variety of compounds were evaluated; xylazine alone, fentanyl alone, a combination of both, as well as xylazine following pretreatment with atipamezole, an α2-adrenergic receptor antagonist. Xylazine (5 mg/kg i.p.) significantly enhanced dopamine release in the NAc, while simultaneously decreasing locomotor activity. Pretreatment with atipamezole (2 mg/kg i.p.) 20 minutes prior to xylazine (5 mg/kg i.p.) attenuated xylazine’s effects on dopamine as well as locomotor activity, suggesting a dependance on α2-adrenergic receptor signaling for this novel effect by xylazine. Fentanyl (0.5 mg/kg i.p.) significantly increased both dopamine levels and locomotor activity, as expected. When xylazine and fentanyl (5 and 0.5 mg/kg i.p., respectively) were administered, we observed an augmented dopamine release that suggested an additive interaction between these drugs, with dopamine having higher and more sustained levels. While the locomotor activity was as expected from xylazine and fentanyl, the effect on dopamine by xylazine alone or in combination with fentanyl, revealed a novel neurochemical effect that may provide insight into the clinical treatment of xylazine and fentanyl-xylazine exposure. These results can inform and guide the development of targeted interventions aimed at mitigating the public health impact of opioid and xylazine co-abuse.

Disclosures: J.R. Trinko: None. **E. Foscue:** None. **E. Kong:** None. **A. Basu:** None. **A. Corstens:** None. **S.L. Thompson:** None. **A.P. Kaye:** None. **J. Taylor:** None. **R.J. DiLeone:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR362.12/P7

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH DA057418
McManus Foundation
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Title: Determination of the role of ventral tegmental area Neuromedin-s expression and cellular activity in morphine behavior

Authors: *C. M. RIVERA QUILES[1], O. DODSON[1], S. FERNANDEZ[3], M. ALDAY[1], K. MCGRATH[1], S. C. SIMMONS[1], B. JUAREZ[3], M. S. MAZEI-ROBISON[2];
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Abstract: Opioid dependence and addiction are a major health and economic burden, but our limited understanding of the underlying neurobiology limits better interventions. Alteration in the activity and output of dopamine (DA) neurons in the ventral tegmental area (VTA) is known to contribute to drug effects, but the mechanisms underlying these changes remain relatively unexplored. We used TRAP to identify gene expression changes in VTA DA neurons following chronic morphine and found that Neuromedin S (NMS) is enriched in VTA DA neurons, and its expression is robustly increased by morphine. However, whether all VTA DA neurons express NMS, and their potential functional impact has yet to be determined. We used conditional DREADD viruses in NMS-Cre mice to manipulate VTA NMS neuronal activity. We found that activation and inhibition of VTA NMS neuronal activity promotes and attenuates morphine-elicited behavior, respectively. However, we have yet to determine the necessity of VTA NMS expression in these behaviors. We hypothesize that NMS expression in VTA DA neurons enhances morphine responses. To test this, we designed a Cre-dependent CRISPR/Cas9 viral vector to knockout NMS expression in VTA DA neurons (via infusion into DAT-Cre mice). Following validation, we will assess the necessity of VTA DA neuron NMS expression for morphine-induced locomotor activity and morphine conditioned place preference (CPP). As an alternative approach, we have also created two NMS transgenic mouse lines. We have developed a constitutive NMS KO mouse line as well as floxed-NMS line. Using these mice, we will be able to assess the effect of whole body and brain region/cell type-specific NMS KO on morphine responses Our initial experiments show that constitutive NMS KO does not affect baseline locomotor activity, anxiety-like behavior, or sucrose preference. Future experiments will assess the effect of constitutive and local KO (via Cre-mediated deletion) on morphine behavior. Together, our studies will determine whether VTA NMS is critical for morphine responses and whether regulation of this neuropeptide may provide a novel avenue to pursue for therapeutic intervention.

Disclosures: C.M. Rivera Quiles: None. **O. Dodson:** None. **S. Fernandez:** None. **M. Alday:** None. **K. McGrath:** None. **S.C. Simmons:** None. **B. Juarez:** None. **M.S. Mazei-Robison:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

Location: MCP Hall A

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Program #/Poster #: PSTR362.13/P8

Topic: G.09. Drugs of Abuse and Addiction

Support: 2T32MH067564 (NISTP T32)
R01 NS122840
Whitehall Foundation

Title: The role of striatal μ-opioid receptors in opioid-driven striatal dynamics and behavior

Authors: *X. WU[1,2], B. YANG[1], S. FLEPS[1], J. ANAIR[1,2], M. V. CENTENO[1], A. V. APKARIAN[1], J. G. PARKER[1];
[1]Neurosci., [2]Interdepartmental Neurosci. Program, Northwestern Univ., Chicago, IL

Abstract: Environmental stimuli associated with drug use can become powerful triggers for drug-seeking behavior. Specifically, opioid-induced dopamine release is thought to reinforce the environmental stimuli and actions associated with opioid administration by modifying the neural circuits underlying motivated behavior—a process that is not fully understood. One of the involved circuits is the dorsal striatum, which has long been recognized as an important hub for reinforcement learning and action selection. The dorsal striatum is densely innervated by midbrain dopamine neurons and itself expresses the receptor for opioids (μORs), which are specifically enriched in the striosomal compartment. μOR-expressing, striosomal neurons preferentially project back to the midbrain dopamine neurons, while neighboring μOR-lacking neurons in the matrix have more canonical direct and indirect basal ganglia pathway projections. Because μORs are inhibitory, opioids are predicted to inhibit striatal striosomal neurons. This in turn is predicted to disinhibit striatal matrix and midbrain dopamine neurons. This milieu, dopamine release and disinhibited striatal activity, could be a recipe for pathological drug-seeking behavior. To test these ideas, we have integrated a dual-color, somatic calcium imaging with two-photon microscopes to simultaneously record activity in μOR-expressing and μOR-lacking dorsal striatal neurons in mice following acute administration of morphine. We have also developed viral genetic approaches to determine whether μOR expression in different striatal subregions is necessary and sufficient for morphine-induced dopamine release and/or conditioned place preference. By characterizing the cell-type-specific dynamics of an important, habit-associated brain region in opioid reinforcement, our experiments contribute to our basic knowledge of the neural substrates underlying the transition to compulsive opioid use.

Disclosures: X. Wu: None. **B. Yang:** None. **S. Fleps:** None. **J. Anair:** None. **M.V. Centeno:** None. **A.V. Apkarian:** None. **J.G. Parker:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR362.14/P9

Topic: G.09. Drugs of Abuse and Addiction

Title: Examining the impact of post-weaning social isolation on oxycodone sensitization

Authors: *E. ENGLISH;
Temple Univ., Philadelphia, PA

Abstract: Adolescence is a crucial period for psychosocial development. Chronic stress and isolation during this period can disrupt normal development and increase substance use behaviors in adulthood. Our lab has established a model of post-weaning social isolation that leads to increased motivation for cocaine and increased cocaine seeking. However, the impact of social isolation on opioid behavioral phenotypes is less clear. The current study aims to explore this by examining the effect of adolescent social isolation on locomotor sensitization at multiple doses of oxycodone. Specifically, we examine the impact of adolescent social isolation on locomotor activity in male and female mice following daily experimenter administered oxycodone. Male and female mice exposed to adolescent social isolation, exhibited a heightened locomotor response to an acute injection of 5mg/kg oxycodone compared to group housed controls on day one. However, after five daily injections of oxycodone, these group differences were no longer present. Group housed control and adolescent socially isolated mice exhibit oxycodone sensitization over the five days of oxycodone administration. We next examined a lower dose of oxycodone to determine if the lack of effect of housing condition on oxycodone sensitization at 5mg/kg was due to a ceiling effect. At the 2.5mg/kg dose, we do not see any impact of housing condition, nor do we detect a significant sensitization over the course of the five daily injections in any experimental group. As the current studies were performed during the light cycle, studies are ongoing to examine oxycodone sensitization in animals during their active phase.

Disclosures: E. English: None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

Location: MCP Hall A

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Program #/Poster #: PSTR362.15/P10

Topic: G.09. Drugs of Abuse and Addiction

Title: Effects of adolescent social isolation on opioid anti-nociception and microglial morphology in the periaqueductal gray.

Authors: *S. OQUENDO[1], B. RHOADS[1], C. SCHULDT[2], B. ARMSTRONG[3], L. A. BRIAND[4];

[1]Temple Univ., Philadelphia, PA; [2]Temple Univ. Grad. Neurosci. Program, Philadelphia, PA; [3]Temple Univ., Bristol, PA; [4]Psychology, Temple Univ., Philadelphia, PA

Abstract: *Effects of adolescent social isolation on opioid anti-nociception and microglial morphology in the periaqueductal gray.*
Oquendo, S, Schuldt, C.B, Rhoads, B.T., Armstrong, B.J., Briand, L.A.
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Early life stress is associated with a wide range of psychiatric and behavioral problems. A common form of early life stress is adolescent social isolation, which alters pain perception and increases the incidence of chronic pain, especially in women. Further, stress can accelerate opioid analgesic tolerance. As social isolation also increases vulnerability to substance use disorder, accelerated tolerance to the analgesic actions of opioids places these individuals at even greater risk. We have established an adolescent social isolation model in mice that leads to accelerated anti-nociceptive tolerance to oxycodone, particularly in female mice. The current studies aim to explore a potential mechanism for these behavioral results by examining the role of microglia in the periaqueductal gray (PAG). Microglia, particularly with the PAG, play a critical role in opioid anti-nociceptive tolerance. We first examined brains for behaviorally naïve mice that had been exposed to either control group housing conditions or adolescent social isolation at weaning (PND21). Using immunohistochemistry, we labeled microglia in the PAG with ionized calcium-binding molecule 1 (Iba1). While we did not see an effect of adolescent social isolation on microglia cell density, we did see alterations in microglial cell morphology using IMARIS imaging software. Studies are underway to examine the interaction between adolescent social isolation and chronic oxycodone administration on microglial cell density and morphology.

Disclosures: S. Oquendo: None. **B. Rhoads:** None. **C. Schuldt:** None. **B. Armstrong:** None. **L.A. Briand:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR362.16/P11

Topic: G.09. Drugs of Abuse and Addiction

Support: 5R37DA039997

Title: Allosteric Modulation of Opioid Receptors in a Mouse Model of Opioid Withdrawal

Authors: *D. K. JESSUP[1], J. R. TRAYNOR[2];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Pharmacol., Univ. of Michigan Med. Sch., Ann Arbor, MI

Abstract: Major contributors to continuing drug use in opioid use disorder (OUD) are the physical and mood changes (anhedonia) occurring in opioid withdrawal syndrome or OWS.

Additionally, chronic opioid use can result in increased sensitivity to pain (hyperalgesia). Proper management of OWS is an important unmet medical need and a significant barrier to discontinuing opioid use (Pergolizzi et al., 2019). We have previously described a positive allosteric modulator of the mu-opioid receptor (MOR-PAM), BMS-986122 (BMS122). BMS122 acts at a distinct site on MOR to enhance the potency and or efficacy of orthosteric agonists. We have further shown these compounds increase the activity of endogenously released opioid peptides at MOR. In contrast these compounds administered alone do not cause respiratory depression, constipation, or reward (Kandasamy et al., 2021). We hypothesized that BMS122 would enhance the activity of MOR agonists and relieve opioid-induced somatic and behavioral symptoms resulting from opioid withdrawal, such as hyperalgesia. Using an in-vitro functional assay of G-protein coupled receptor activation (GTP $\gamma^{35}S$) at human opioid receptors expressed in CHO cells we show that BMS122 (10M) as expected enhances the activity of the enkephalin derivative MOR peptide DAMGO (48.6 nM ± 6.4 DAMGO vs 9.5 nM ± 0.7 DAMGO+BMS122) but does not significantly shift the potency of the endogenous kappa-opioid (KOR) ligand dynorphin 1-17 (0.68 nM ± 0.3 dynorphin vs 0.44 nM ± 0.1 dynorphin + BMS122). These data suggest BMS122 would enhance the activity of endogenous opioid peptides at MOR to relieve withdrawal symptoms without exacerbating dynorphin-mediated withdrawal-behaviors. Effects of BMS122 on spontaneous and naloxone precipitated withdrawal following repeated opioid exposure utilizing male and female CD1 mice will be presented. Allosteric modulation of MOR may provide a therapeutic strategy to ameliorate withdrawal-induced physical and mood-altering symptoms which are a significant clinical challenge to managing OWS.

Disclosures: D.K. Jessup: None. **J.R. Traynor:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR362.17/P12

Topic: G.09. Drugs of Abuse and Addiction

Title: In vivo calcium imaging to shed light on prefrontal cortical neurocircuitry alterations during opioid use and withdrawal

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Abstract: *In 2020, the United States National Institute on Drug Addiction reported approximately 2.7 million US citizens over the age of 12 had an opioid use disorder (OUD) in the past 12 months. Of this, 2.7 million, 2.3 million individuals had a prescription opioid use disorder. It is imperative for researchers apply new technologies to further unravel the secrets behind OUD and its complex mechanism and bring forth novel therapies to treat patients best in an individualistic manner. In vivo single photon calcium imaging in awake freely behaving mice*

is an innovative tool that has proven beneficial in examining neuronal activity and behavior in a variety of fields. Implementation of this technology allows for a more comprehensive understanding of OUD thus providing leads for novel therapeutics. The prefrontal cortex is a critical brain region in circuits underlying both reward and anxiety. A high anxiety phenotype is frequently reported in patients suffering from opioid withdrawal and is also listed as a principal culprit for return to use. Using in vivo calcium imaging, we observe not only aberrant firing patterns present with periods of acute to chronic opioid use but also alterations to firing coordination with mice presenting an anxiety-like response while experiencing opioid withdrawal during behavioral assays frequently used to asses anxiety-like responses in preclinical models, open field and elevated zero maze. Perineuronal nets (PNNs) are primarily formed throughout development and are considered a contributing factor to maintaining synaptic rigidity in the adult brain. Synaptic plasticity has been an area of interest to substance use disorder (SUD) researchers, as an increase in synaptic plasticity is observed in SUD patients and this is thought of as a driving force in habit forming and SUDs. Lastly, cellular communication between the sheath that is PNNs, and microglia is an area lacking in information and will provide interesting insights into the functions of both PNNs and microglia in an OUD brain. The lasting effects of chronic opioid exposure are evident in neuronal firing rate and synaptic plasticity with a mediator of this mechanism being microglia's effects on perineuronal nets.

Disclosures: A. Alsum: None. **J.R. Turner:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA Grant U01DA045300
NIDA Grant T32DA007288-30
NIDA Grant K99DA057390

Title: Distinct alterations in synaptic plasticity associated with heroin vulnerability versus resiliency

Authors: *B. N. KUHN[1], S. J. WALTERHOUSE[1], J. L. HOPKINS[1], R. HODEBOURG[2], A. A. PALMER[3], C. GARCIA-KELLER[4], P. W. KALIVAS[5];
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Abstract: Due to the rise of opioid use disorder (OUD) worldwide it is imperative to disentangle the behavioral and neurobiological correlates associated with both vulnerability and resiliency. Using a novel preclinical rodent model of OUD that captures the multi-symptomatic diagnosis and complex multidimensional interactions between symptoms conferring OUD vulnerability versus resiliency, we have shown distinct behavioral and neurobiological profiles associated with each phenotype. Furthermore, we have shown marked sex differences within phenotypes for these measures. Genome-wide association study (GWAS) analysis indicates both resiliency and vulnerability to OUD are heritable states, and furthermore identified genetic variants involved in neuroplasticity which have been implicated in OUD as well. These findings prompted further investigation into mechanisms of synaptic plasticity underlying vulnerability and resiliency within the nucleus accumbens core (NAcc). Alterations in NAcc dendritic spine head diameter and density are associated with changes in synaptic strength and are observed following opioid withdrawal and brief cued reinstatement tests. Contrary to expectations, no differences in spine morphology are observed following cued reinstatement in either behavioral phenotype. However, there is a vulnerable phenotype female-driven suppression of NAcc spine density following protracted abstinence. These conflicting results may be due to unknown composition of D1- vs D2-MSN quantification, as these cell types exhibit opposing regulation of drug-seeking behavior and is currently under investigation. Additional forms of synaptic plasticity were also assessed as GWAS results suggested alterations in microglial reactivity and extracellular matrix (ECM) composition may contribute to OUD vulnerability. Phenotypic differences in NAcc microglial reactivity were observed with current analyses assessing differences in other brain regions. Microglial functionally alter ECM composition thereby affecting synaptic plasticity. Results show that perineuronal nets (PNNs), one component of the ECM whereby degradation is associated with experience-dependent learning, also show phenotypic differences. Current data suggests greater prelimbic cortex PNN degradation associated with OUD resiliency. These data, guided by GWAS findings, highlight distinct alterations in synaptic plasticity associated with both OUD vulnerability and resiliency and warrant further investigation.

Disclosures: B.N. Kuhn: None. **S.J. Walterhouse:** None. **J.L. Hopkins:** None. **R. Hodebourg:** None. **A.A. Palmer:** None. **C. Garcia-Keller:** None. **P.W. Kalivas:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Program #/Poster #: PSTR362.19/Q2

Topic: G.09. Drugs of Abuse and Addiction

Support: DA000069
NIH / NIDA IRP

Title: A Novel Etonitazene Analog Metabolite with High Selectivity for Mu Opioid Receptors

Authors: *J. GOMEZ, Z. FRANGOS, R. BUDINICH, A. SULIMA, S. HUBBARD, M. H. BAUMANN, K. C. RICE, M. MICHAELIDES;
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Abstract: Opioid drugs have been utilized and extensively researched due to their pain-relieving characteristics, and synthetic mu opioid receptor (MOR) agonist drugs represent the most potent analgesics currently accessible. Nonetheless, these medications are associated with recognized negative consequences, such as respiratory depression and the potential for abuse. We have characterized a novel etonitazene analog (fluornitrazene (FNZ)) and found favorable qualities, such as, MOR selectivity, a high therapeutic index, and low potential for tolerance. However, the kinetics of FNZ did not agree with the behavioral phenotypes observed. We examined the major metabolite of FNZ, desethyl-FNZ (DFNZ), and characterized this compound using the same methods. We found similar qualities of DFNZ as compared to FNZ, however, the affinity for MOR was 10-fold higher and larger doses were necessary to elicit analgesic effects. To date we have not found evidence that DFNZ enters the brain, and we predict that the metabolite is restricted to the periphery. The working hypothesis is that based on the pharmacokinetics of both drugs, FNZ may be responsible for immediate analgesic efficacy and DFNZ may be responsible for prolonged analgesia. The importance of this finding is that we have discovered an opioid that is peripherally restricted and may provide long-lasting analgesia and low abuse liability. Ongoing experiments aim to test the abuse liability of DFNZ using established preclinical models.

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Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Topic: G.09. Drugs of Abuse and Addiction

Support: DA050908
DA056804

Title: Insulin-like growth factor 1 and its receptor in prefrontal cortex regulates heroin addiction-induced behavioral and synaptic plasticity

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Abstract: Opioid use disorder (OUD) is a chronic, relapsing mental illness characterized by compulsive drug seeking and vulnerability to relapse. However, the understanding of the

neurobiology of OUD is still unclear. Clinical studies show that the neuronal responses to stimuli in the prefrontal cortex (PFC) from individuals with OUD are disrupted. Consistently, preclinical data also report opioid-induced synaptic dysfunction in the PFC. Given the critical role of PFC in regulating opioid-related behaviors, it is vital to investigate the molecular mechanisms underlying opioid-induced PFC dysfunction and its role in shaping opioid-induced behavioral plasticity. Increasing studies have shown that insulin-like growth factor 1 (IGF1) and IGF1 receptor (IGF1R) regulate synaptic transmission, but the involvement of IGF1/IGF1R in opioid addiction-induced synaptic deficits remains unknown. Here we used a mouse heroin self-administration (SA) model to investigate the role of IGF1/IGF1R on heroin-induced behavioral and synaptic plasticity. We first found that IGF1/IGF1R and its downstream signaling in PFC were decreased after prolonged abstinence from heroin SA. Moreover, intra-PFC IGF1 administration attenuated while IGF1R selective knockdown in PFC pyramidal neurons potentiated heroin-seeking behavior, heroin motivation and dose response. Furthermore, we used whole-cell patch-clamp method and in-vivo Ca^{2+} imaging to detect changes in synaptic plasticity and neural activity. Our data showed that intra-PFC IGF1 administration restored heroin abstinence-induced decrease in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor- and N-methyl-D-aspartate (NMDA) receptor-mediated evoked excitatory postsynaptic currents (eEPSCs). In addition, IGF1 recovered the elevated AMPA/NMDA ratio in response to heroin-associated cues in mice underwent heroin abstinence. In-vivo Ca^{2+} imaging results also showed that IGF1 attenuated heroin abstinence-induced increase in neural activity. These data indicate that IGF1/IGF1R system in the PFC plays a key role in regulating heroin-induced behavioral and synaptic plasticity, which will provide a novel therapeutic target for the development of OUD treatment strategies.

Disclosures: S. Yue: None. **Y. Wang:** None. **Z. Wang:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Topic: G.09. Drugs of Abuse and Addiction

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F31 DA058451
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Title: Unraveling the role of interpeduncular nucleus glucagon-like peptide-1 receptor agonism in fentanyl-induced striatal dopamine signaling

Authors: *A. POTHIKAMJORN[1], R. HERMAN[2], H. D. SCHMIDT[3];
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Abstract: In the United States, fatal opioid overdose continues to be one of the leading causes of preventable death. In 2021, over 60% of drug overdose deaths were associated with fentanyl or its analogs. Thus, it is critical to understand the central mechanisms underlying fentanyl seeking, which may further the development of novel effective treatments for fentanyl use disorder (FUD).
Our lab has shown that glucagon-like peptide-1 receptor (GLP-1R) activation in the interpeduncular nucleus (IPN) reduces fentanyl-seeking behavior in rats. GLP-1R-expressing inhibitory IPN neurons project to the laterodorsal tegmental nucleus, which is important for opioid-mediated dopamine release, and preferentially sends excitatory signals to ventral tegmental area dopaminergic neurons. These cells then project to the nucleus accumbens (NAc). Several studies suggest that dopamine release in the NAc plays a role in opioid-mediated behavior. For example, acute opioid injection during abstinence increases dopamine release in the NAc which is necessary for drug-primed reinstatement of opioid seeking. Consistent with these results, administration of a dopamine receptor antagonist attenuates heroin-primed drug reinstatement. Given that 1) NAc dopamine signaling is important for opioid-primed reinstatement, 2) GLP-1Rs are expressed on IPN neurons projecting to regions that modulate opioid-mediated dopamine release, and 3) IPN GLP-1R activation attenuates fentanyl reinstatement, we hypothesized that IPN GLP-1R activation will reduce NAc dopamine signaling in response to an acute injection of fentanyl.
To record dopamine signaling using fiber photometry in male and female rats, we infused an adeno-associated virus expressing GRAB_DA1h into the NAc and implanted an optic fiber directly above the viral infusion site. We also implanted bilateral guide cannula aimed at the IPN and a jugular catheter for intravenous infusion of fentanyl. In each test session, we injected the GLP-1R agonist Exendin-4 (Ex-4) (0 or 0.1 μg) into the IPN immediately before fiber photometry recordings. After ten minutes of recording, we administered an acute infusion of fentanyl (0 or 5 μg/kg, i.v.) and continued recording for ten minutes. We utilized a within-subjects design with counterbalanced treatment order. We showed that 5 μg/kg fentanyl (i.v.) increased dopamine sensor fluorescence in the NAc. We are currently analyzing the effect of intra-IPN Ex-4 on fentanyl-induced dopamine release. This study explores the complex role of the IPN and IPN GLP-1Rs in fentanyl-mediated dopamine signaling and may provide further support for using GLP-1R agonists as a treatment for FUD.

Disclosures: A. Pothikamjorn: None. **R. Herman:** None. **H.D. Schmidt:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH R21DA054693

Title: Mu opioid receptor activation potentiates excitatory transmission at the habenula-peduncular synapse

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Abstract: The continuing opioid epidemic poses a huge burden on public health. Identifying the neurocircuitry involved and how opioids modulate their signaling is essential for developing new therapeutic strategies. The medial habenula (MHb) is a small epithalamic structure that expresses high levels of mu-opioid receptors (MORs) and projects primarily to the interpeduncular nucleus (IPN). Recent in-vivo reports implicate the MHb-IPN circuit in opioid withdrawal and anxiety-related behaviors; however, little is known on how opioids/MOR affect excitability or neurotransmission in this pathway. Using MOR reporter mice, we observed that MOR-expressing cells localize to lateral MHb and co-localize with glutamatergic markers. Expression of ChR2: mCherry in the MHb of *Oprm1*-Cre mice revealed robust projections in the rostral and lateral subregions of IPN. We used whole cell patch-clamp to record from rostral IPN neurons and optogenetics to activate MHb inputs and evoke fast excitatory post-synaptic currents (oEPSCs) that were sensitive to glutamate receptor blockers. Surprisingly, bath application of the MOR agonist DAMGO significantly potentiated oEPSC amplitude. This DAMGO-mediated potentiation persisted in the presence of GABA receptor blockers, and in the presence of tetrodotoxin (TTX) + 4-aminopyridine (4-AP). These results suggest that the faciliatory effects of DAMGO on excitatory transmission were not polysynaptic but isolated to the MHb-IPN synapse. In addition, in a subset of rostral IPN neurons DAMGO induced an outward current, consistent with a GIRK-mediated hyperpolarizing conductance. DAMGO application also led to a decreased frequency of spontaneous excitatory post-synaptic currents (sEPSCs) in rostral IPN, indicating that these cells receive excitatory inputs that can be inhibited by MOR activation. Overall, our results suggest that MORs are a) expressed in a subset of rostral IPN neurons and excitatory inputs where they drive canonical inhibitory pre-synaptic and post-synaptic effects; b) expressed in a subset of MHb axon terminals where their activation induces a non-canonical faciliatory effect on glutamatergic synaptic transmission. Future work may reveal how acute effects of opioids in the habenulo-peduncular circuit contribute to opioid-induced behaviors, or how opioid-induced plasticity in this circuit contributes to opioid dependence and withdrawal.

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Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR362.23/Q6

Topic: G.09. Drugs of Abuse and Addiction

Support: CAPPI Pilot Grant

Title: Acute morphine and glucocorticoid signaling regulate heat shock gene expression in astrocytes

Authors: *A. CLEERE[1], R. A. PHILLIPS, III[2], G. TWA[3], N. ROBINSON[4], L. IANOV[5], R. E. SORGE[6], J. J. DAY[4], J. J. TUSCHER[7];
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Abstract: Acute morphine and pain have been shown to induce transcriptional changes in the ventral tegmental area (VTA), a brain structure important in drug-seeking behavior, both *in vivo* and *in vitro*. We recently used single-nucleus RNA sequencing (snRNA-seq) in the VTA of adult rats to identify cell-type specific changes in gene expression after acute morphine experience in a chronic pain model. Surprisingly, we found that glial cell populations, which are non-neuronal cells that help support neuron function, had more changes in gene expression than neuronal cell populations. Astrocytes, a type of glial cell, were particularly transcriptionally responsive to acute morphine and showed strong induction of *Fkbp5*, regardless of pain state. Previous literature has implicated glucocorticoid receptors (GR) in pain responses and transcriptional changes of *FKBP5*. Here, we employed a human-derived astrocyte cell culture system to investigate the mechanisms behind opioid and glucocorticoid-induced changes in gene expression. We differentiated neural progenitor cells into astrocytes and delivered pharmacological treatments. Astrocyte treatment with DAMGO, a mu opioid receptor antagonist, did not alter *FKBP5* expression. In contrast, treatment with either the endogenous glucocorticoid cortisol, or the GR agonist dexamethasone, both increased *FKBP5* expression in astrocytes. Pretreatment with the GR antagonist mifepristone blocked cortisol and GR agonist-induced transcriptional changes. These findings suggest GR, not mu opioid receptor, activation is both sufficient and necessary to induce *FKBP5* expression in astrocytes. We are currently working on validation of a CRISPR interference (CRISPRi) tool for selective repression of *NR3C1*, which encodes the GR, in astrocytes to further investigate how GR signaling mediates opioid-induced transcriptional responses.

Disclosures: A. Cleere: None. **R.A. Phillips:** None. **G. Twa:** None. **N. Robinson:** None. **L. Ianov:** None. **R.E. Sorge:** None. **J.J. Day:** None. **J.J. Tuscher:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Program #/Poster #: PSTR362.24/R1

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant 5U01DA051947-04

Title: Title: A single-cell multi-omic and spatial transcriptomic atlas for the effects of heroin self-administration and abstinence on cell types in the ventral pallidum

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Abstract: Opioid addiction is characterized by the persistence of drug-craving even after long periods of abstinence, leading to recurring cycles of drug-seeking and relapse. The ventral pallidum (VP) may play an important role in these processes as a central node of both the mesolimbic reward system and of extended amygdala circuits activated during withdrawal. However, the cell type diversity of the VP and the molecular adaptations associated with substance use and addiction are poorly characterized. To address this, we sequenced the nuclear transcriptomes (snRNAseq) of 92,978 cells and chromatin accessibility states (snATAC-seq) of 47,050 cells from the VP of rats in the context of heroin self-administration and forced abstinence. We generated a multimodal atlas for the diversity of neuronal and non-neuronal cells including 48 transcriptionally distinct neuronal subtypes in the VP and surrounding regions. We verified the spatial localizations of these cell types within the VP and surrounding regions via subcellular-resolution spatial transcriptomics using the CosMx platform. We characterized cell type-specific changes in gene expression and chromatin accessibility in rats from a heroin self-administration scheme vs. controls at 1 or 14 days of forced abstinence to gain insight into both acute and persistent effects on gene regulation. Gene co-expression network analyses revealed distinct changes in GABAergic vs. glutamatergic neurons within the VP. We integrated snRNA-seq and snATAC-seq data to model gene regulatory networks mediating the effects of heroin on neuroplasticity and neuroinflammation. Our results provide insight into the gene regulatory mechanisms mediating the persistent effects of opioids through the VP. The identification of high-impact high-specificity transcriptional mechanisms will open promising new avenues for treatment research.

Disclosures: B. Grissom: None. **M.E. Cortes-Gutierrez:** None. **S. Mitra:** None. **M. Green:** None. **S.A. Ament:** None. **D.M. Dietz:** None. **M. Lobo:** None.

Poster

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA P01DA047233
NIDA R01DA014133

Title: Transcriptional effects of fentanyl versus morphine exposure and withdrawal in reward-associated regions of the brain

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Abstract: Opioid use disorder (OUD) underlies a detrimental public health crisis leading to tens of thousands of deaths per year in the U.S. In recent years, the opioid crisis has become predominantly fueled by synthetic opioids such as fentanyl. The majority of investigations into the transcriptional and epigenetic effects of opioids on the brain, however, have been conducted using naturally derived opioids and their congeners such as morphine and heroin. Fentanyl has unique structural and pharmacokinetic properties compared to the other opioids and has been shown to bind additional pockets within the mu opioid receptor (MOR). MOR also has the potential to activate several signaling pathways, and the downstream molecular consequences of the differential binding of synthetic versus non-synthetic opioids at this receptor are unknown. In this study, we are investigating the transcriptional and epigenetic effects of chronic exposure to fentanyl on reward-related brain regions and identifying the unique molecular effects of fentanyl compared to morphine that may result from its differential functional properties. We used conditioned place preference (CPP) as an indirect measure of drug reward to identify an equally rewarding dose of fentanyl (0.2 mg/kg) and morphine (10 mg/kg) when injected intraperitoneally (IP) in wildtype male C57BL/6J mice. Using these doses, we carried out a chronic drug exposure and withdrawal paradigm with daily IP injections for 10 days followed by a withdrawal period of either 24 hours or 30 days. Data from bulk mRNA sequencing of the nucleus accumbens (NAc) and ventral tegmental area (VTA) were analyzed to reveal the transcriptional changes resulting from exposure to and withdrawal from fentanyl compared to morphine and a saline control group. Our findings indicate that synthetic opioids exert some unique transcriptional effects on these brain reward regions and suggest further epigenetic investigations to uncover the mechanisms behind these differences.

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Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01DA04055
NIH Grant R01DA049139

Title: Characterizing rat corticolimbic activity associated with inhibition of heroin seeking during extinction

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Abstract: Evidence indicates that theta oscillations in the rat infralimbic cortex (IL) are associated with inhibition of cocaine seeking during extinction; however, the role of the IL in extinction of opioid seeking is unclear. Moreover, it is unknown whether the IL interacts with other corticolimbic structures implicated in regulation of opioid seeking, such as the anterior insular cortex (aIC) and basolateral amygdala (BLA), during extinction. To address these questions, we used in vivo electrophysiology to simultaneously record neural activity from the IL, aIC, and BLA during heroin self-administration and extinction training. Four adult male Sprague-Dawley rats learned to self-administer heroin intravenously on a high-to-low tapered FR1 schedule, decreasing heroin dosage every two sessions until arriving at 0.014 mg/kg/infusion. Rats then proceeded to 2-hour trial-based sessions, wherein a lever producing a heroin infusion and light and tone cues was only available during specific signaled trials. This created epochs of heroin-seeking behavior, or inhibition thereof, around which electrophysiological data could be analyzed. After at least 10 days of self-administration, rats were fitted with a custom-designed three-site, 96-channel microdrive array (9 tetrodes/site), with tetrodes lowered into the IL, aIC, and BLA. Rats proceeded with recorded self-administration, followed by at least 5 days of recorded extinction sessions wherein lever presses during a trial had no consequence. Single-unit and local field potential (LFP) data was collected from each tetrode and analyzed for each region during the last self-administration session and early and late extinction sessions.
Analyses focused on group-level changes in LFP frequency power around trial onset and lever presses during extinction. Findings indicate that theta- and alpha-band oscillations in the IL, aIC, and BLA are sensitive to trial onset and heroin-seeking behavior, and that this activity changes across extinction learning. Ongoing work is investigating whether coherence between regions is associated with heroin seeking, or inhibition thereof. Overall, these findings suggest that IL-aIC-BLA circuitry comprises a dynamic network during extinction of heroin seeking.

Disclosures: M.S. McGregor: None. **S.J. Farley:** None. **J. Kim:** None. **R.T. LaLumiere:** None.

Poster

PSTR362: Opioids: Cell Signaling, Circuitry, and Neurophysiology

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Program #/Poster #: PSTR362.27/R3

Topic: G.09. Drugs of Abuse and Addiction

Support: Gruber Science Fellowship
Kavli Award for Postdoctoral Diversity
DP1-DA050986

Title: Cortical brain areas involved in contextual tolerance to fentanyl in male C57BL/6 mice

Authors: *R. G. SERRANO, R. PEREZ, M. PICCIOTTO;
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Abstract: Drug overdose deaths continue to rise across the United States with the majority of these deaths involving synthetic opioids such as fentanyl. Consistent opioid exposure results in tolerance to these drugs and an extensive literature has identified cellular and molecular pathways underlying this tolerance. Interestingly, despite profound molecular changes, opioid tolerance can be reversed when the drug is administered in an unexpected context. The mechanisms underlying context-dependent tolerance and its reversal are much less studied. Work in our laboratory has identified a set of brain regions that are active, as measured by immediate early gene expression, during exposure to fentanyl in a previously fentanyl-paired environment, and a separate set of brain areas that are active when fentanyl is administered in a previously saline-paired environment. In order to determine whether these brain areas are causally involved in contextual tolerance or its reversal, we measured fentanyl-induced analgesia in the hotplace test. We used an alternating schedule of saline and fentanyl administration in different environments, measured fentanyl tolerance in the fentanyl-paired context on the last day of administration, and then measured tolerance reversal by administering fentanyl in the previously saline-paired environment. To evaluate the role of specific brain areas identified in the anatomical study, we used a chemogenetic strategy to inhibit the anterior cingulate cortex or the perirhinal cortex during tolerance and tolerance reversal, respectively, using a virally-encoded Gi-coupled DREADD in C57BL/6 mice. We found that inhibiting the anterior cingulate during fentanyl administration in a fentanyl-paired context could decrease analgesic tolerance, whereas inhibiting the perirhinal cortex during fentanyl exposure in a saline-paired environment was not sufficient to induce contextual tolerance. These studies confirm that circuit-level changes mediate contextual tolerance to opioids and begin to identify cortical areas responsible for contextual tolerance.

Disclosures: R.G. Serrano: None. **R. Perez:** None. **M. Picciotto:** None.

Poster

PSTR363: Prefrontal Mechanisms in Non-Human Primates

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Program #/Poster #: PSTR363.01/R4

Topic: H.04. Executive Functions

Support: ONR MURI N00014-23-1-2768
The JPB Foundation
The Picower Institute for Learning and Memory

Title: Prefrontal theta governs working memory retrieval

Authors: *H.-B. HAN[1,3], S. L. BRINCAT[2], T. BUSCHMAN[4], E. K. MILLER[1];
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Abstract: Neural representations of items in visual working memory (VWM) seems to wax and wane over time. Here, we report that the phase of prefrontal theta (3-6 Hz) governs the temporal variation of VWM. We found monkeys' VWM task performance in multi-item delayed match-to-sample task was modulated by the ongoing phase of prefrontal theta at the time of VWM retrieval (i.e., test display onset timing). Reaction time (RT) was slower and hit rate was lower during the rising phase ("poor phase") of theta. By contrast, RT was faster and the hit rate was higher during the falling phase ("good phase") of theta. We also observed theta-rhythmic phasic inhibition of cortical excitability. The strongest inhibition of prefrontal spike rates was around the "good phase" while inhibition was weakest around the "poor phase". Furthermore, theta power was not only positively correlated with beta power, but also exhibited theta-beta phase-amplitude coupling, resulting in beta being most pronounced during the "good phase" of theta. We also found that microsaccades was suppressed during the "good phase" of theta. Our results suggest that theta, which has been proposed as a rhythm underlying attentional sampling process operates for sampling both external stimuli and internal representations.

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Poster

PSTR363: Prefrontal Mechanisms in Non-Human Primates

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Program #/Poster #: PSTR363.02/R5

Topic: H.04. Executive Functions

Support: ONR: N00014-22-1-2453
NEI: 5R01EY033430-03

Title: Neural dynamics underlying target tracking across hemifields

Authors: *M. BROSCHARD[1], J. E. ROY[2], S. L. BRINCAT[3], M. K. MAHNKE[1], E. K. MILLER[4];
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Abstract: Each hemisphere of the brain primarily processes visual information from the contralateral hemifield. This poses a specific challenge when objects move from one side of vision to the other (e.g., a football being thrown down the field). In this case, there must be a smooth handoff of information from one hemisphere to the other. We trained non-human primates (NHPs) to covertly track moving dots. On each trial, the NHPs were presented with two dots. They were then cued to attend to one of them (i.e., the target) and ignore the other (i.e., the distractor). At random points along their trajectories, the dots changed color (e.g., gray to red). The NHPs were trained to make a saccade to the target when its color changed while ignoring color changes of the distractor. Spiking activity and local field potentials (LFPs) were recorded in the dorsolateral prefrontal cortex (dlPFC) and ventrolateral prefrontal cortex (vlPFC) bilaterally. Beta (15-30 Hz) power and interhemispheric coherence in the dlPFC peaked when the dots were first displayed. Gamma (30-100 Hz) power in the vlPFC peaked when the target was cued and persisted as the target moved along its trajectory. Theta (4-9 Hz) power, spiking activity in the vlPFC, and theta spike-field phase locking conveyed the position of the target throughout the trajectory. Alpha (10-15 Hz) power and interhemispheric coherence ramped up before the hemispheric transfer, peaking just after it. These results suggest that: 1. Beta may be involved in preparation for attentive tracking (a top-down function); 2. Alpha may be involved in transferring the target across hemispheres; 3. Theta/gamma are involved in processing relevant sensory information. 4. The dlPFC is more involved in top-down control while the vlPFC is more involved in bottom-up sensory processing.

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Poster

PSTR363: Prefrontal Mechanisms in Non-Human Primates

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The Simons Center for the Social Brain
The JPB Foundation
The Picower Institute for Learning and Memory
DE-SC0024386

Title: Convergent effects of different anesthetics on changes in phase alignment of cortical oscillations

Authors: *A. BARDON[1], J. J. BALLESTEROS[2], S. L. BRINCAT[3], J. E. ROY[4], M. K. MAHNKE[1], Y. ISHIZAWA[5], E. N. BROWN[6], E. K. MILLER[7];
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Abstract: Many different anesthetics exist and are widely used in medicine for similar purposes, despite having distinct mechanisms of action. The common elements by which these drugs induce similar outcomes, namely loss of responsiveness, is an open question. Their convergence is likely at a higher level, in the network dynamics driven by each drug's unique molecular effects. To explore the convergent effects of these drugs, we examined how ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, and dexmedetomidine, an α2 adrenergic receptor agonist, affected neural oscillations in the prefrontal cortex of nonhuman primates. We analyzed cortical synchrony, which is thought to play a role in consciousness. In addition to quantifying phase locking, a common measure of the consistency of local field potential signals between different areas, we also calculated the phase offsets at which these local field potentials were locked. Previous work has shown that anesthesia increases the phase locking of low-frequency local field potential activity across the cortex. We observed similar increases with anesthetic doses of ketamine and dexmedetomidine in the ventrolateral and dorsolateral prefrontal cortex, both within and across hemispheres. However, the nature of the phase locking varied between regions. We found that oscillatory activity in different prefrontal subregions within each hemisphere became more anti-phase with both drugs. Local analyses within a region suggested that this finding could be explained by broad cortical distance-based effects, such as a large traveling wave. By contrast, homologous areas across hemispheres increased their phase alignment. Analysis of sub-anesthetic doses of ketamine and dexmedetomidine revealed similar but weaker effects in phase offset; however, the lack of broad increase in phase locking suggests that more consistent locking of regions in- and anti- phase is necessary for achieving a state of general anesthesia or unconsciousness. Despite their different mechanisms of action at the molecular level, we found similar network-level effects between the two drugs. Our results suggest that the drugs induce strong patterns of cortical phase alignment that are markedly different from those in the awake state. These dynamics may be a marker of loss of responsiveness and suggest a fundamental role for broad, low-frequency activity in driving and disrupting consciousness.

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Poster

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NEI 1R01EY033430-01A1

The JPB Foundation
The Picower Institute for Learning and Memory

Title: Subspace transformations underlie decision-driven information prioritization

Authors: *H. LI[1], J. M. ROSE[2], S. L. BRINCAT[3], E. K. MILLER[4];
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Abstract: The ability to flexibly select relevant information is critical to intelligent behavior. We are often faced with two or more choices of different values. How the brain represents different options and using their relative value to guide choices is still largely unknown.
We trained non-human primates (NHPs) on a task. They were shown two spatial targets in succession and then learned their relative value. NHPs were then free to choose one of the cues, almost always choosing the higher-value target. We examined spiking activity from the lateral prefrontal cortex.
Subspace analysis revealed information geometry that corresponded to and changed with task demands. Before learning their relative value, both targets were held in memory. They were maintained in separate, near orthogonal subspaces based on their order of appearance, with equal fidelity. Then, after learning their relative value, information about the sequence collapsed into a common location subspace. This allows a single decoder to readout location of chosen target regardless of its order. Both the chosen and unchosen targets were represented in this common subspace. But the chosen target showed greater feature separability. Plus, location of the chosen and unchosen targets were anti-correlated, potentially reducing interference between them. Furthermore, relative differences between the target values modulated their representations. With greater difference there was greater feature separation for chosen targets and the location representations of the chosen and unchosen targets were more anti-correlated. This implies that relative value affects subspace geometry and drives choice in a graded way.
In summary, our results illustrate the dynamic subspace representations supporting information maintenance and selection guided by value decisions. Before the choice, the brain kept track of the two options using orthogonalization. Selection involved projecting both options to a common subspace but with different mapping and expanded features of the chosen option. Selection was not performed in an all-or-none way. The effects on the geometry of the options was graded by the reward difference between the options.

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Poster

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Simons Center for the Social Brain

Title: Layer-specific and high-frequency phase-matched intracortical microstimulation to test the roles of beta and gamma rhythms across cortical circuits

Authors: *A. J. MAJOR, S. L. BRINCAT, M. K. MAHNKE, E. K. MILLER;
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Abstract: Cortical brain rhythms are proposed to influence neuronal circuit function, but testing this proposal is a technical challenge. Precise modulation of specific brain rhythms would allow causal testing of local field potential (LFP) rhythms in cortical circuits. Phase-matched electrical stimulation has previously enhanced or suppressed lower frequency brain rhythms (Knudsen and Wallis, *Neuron*, 2020; Peles et al., *Cell Rep*, 2020), but targeting higher beta and gamma frequencies (> 30 Hz) has remained a challenge. In phase-matched closed-loop stimulation, delivery of stimulation pulses is matched to the precise frequency and phase of endogenous brain rhythms. Closed-loop stimulation is more effective at providing frequency-specific manipulations than open-loop, "blind" stimulation techniques (Widge et al., *PLOS One*, 2018). Open-loop stimulation does not consider endogenous rhythms, akin to pushing a bike pedal at a random time, rather than during its descent.
Our system includes custom-designed Plexon laminar probes with dedicated stimulation/record contacts, custom-designed stim/record headstages from Open Ephys, next-generation ONIX acquisition board, and Bonsai software. Laminar electrodes are aligned across the layers of cortical grey matter online using current source density sink and the spectrolaminar motif. Band-passed LFP signals are monitored and an autoregressive forward prediction is generated (Chen et al., *IEEE Trans Biomed Eng*, 2013) in order to predict delay time before the next target phase. Stimulation pulses (cathodic-leading biphasic waveforms, 0.2 ms total duration) are triggered when power of the targeted frequency band exceeds $z > 2$, thus ensuring a local field potential burst is present.
Our system can perform closed-loop stimulation with high phase specificity across a range of frequency bands, including high-beta and gamma. In pilot experiments, laminar probes recorded activity in rhesus parietal region 7A and delivered phase-specific stimulation with low phase variance across a broad range of target frequencies: 24.3° SD at 10-20 Hz, 21.1° SD at 25-35 Hz, 31.1° SD at 45-55 Hz, 26.2° SD at 65-75 Hz, and 53.8° SD at 85-95 Hz. This system can effectively provide layer-, frequency-, and phase-specific neuromodulation, which can test major theories of brain rhythms in cortical circuits, such as Communication through Coherence, Predictive Routing, and Spatial Computing.

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Poster

PSTR363: Prefrontal Mechanisms in Non-Human Primates

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Topic: H.04. Executive Functions

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Title: Context-dependent flow of beta and gamma waves in models of working memory tasks

Authors: *Z. CHEN, S. L. BRINCAT, E. K. MILLER;
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Abstract: Working memory (WM) is a fundamental cognitive function that allows us to flexibly control our behaviors based on the goal and context. Such flexibility requires the representations of WM content to be reshaped and manipulated by top-down control carrying the context information. Recent work has suggested that this top-down control may stem from the interactions between beta and gamma waves, such that WM content information carried by gamma waves flows spatially across the prefrontal cortex (PFC) in a context-dependent way. However, it remains unclear what neural circuit mechanism could underlie such flexible control of information. To address this question, we built a detailed spiking neural network model of PFC, comprising diverse inhibitory interneuron types. By leveraging these interneurons' contributions in generating brain oscillations, our model faithfully reproduced the dynamics of beta and gamma waves and the empirically observed anti-correlated interactions during WM tasks. Activation of specific inhibitory cells generated context-carrying spatial-temporal patterns of beta waves. These activated inhibitory cells suppressed nearby pyramidal cells, thereby making the beta waves act like spatial stencils on gamma, consistent with predictions of spatial computing theory (Lundqvist et al. 2023). Comparing our model predictions with data from several WM tasks, we found consistent agreement, supporting the validity of our model. Taken together, our findings shed light on the neural mechanisms underpinning flexible WM control and unveil governing principles for the PFC pattern dynamics.

Disclosures: Z. Chen: None. **S.L. Brincat:** None. **E.K. Miller:** None.

Poster

PSTR363: Prefrontal Mechanisms in Non-Human Primates

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR363.07/S4

Topic: H.04. Executive Functions

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NIGMS P01GM118269

The JPB Foundation
The Picower Institute for Learning and Memory

Title: Propofol anesthesia destabilizes neural dynamics across cortex

Authors: *A. J. EISEN[1], L. KOZACHKOV[1], A. BASTOS[2], J. A. DONOGHUE[3], M. K. MAHNKE[1], S. L. BRINCAT[1], S. CHANDRA[1], J. TAUBER[4], E. N. BROWN[5], I. R. FIETE[1], E. K. MILLER[1];
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Abstract: Every day, hundreds of thousands of people undergo general anesthesia. One hypothesis is that anesthesia disrupts dynamic stability, the ability of the brain to balance excitability with the need to be stable and controllable. To test this hypothesis, we developed a method for quantifying changes in population-level dynamic stability in complex systems, Delayed Linear Analysis for Stability Estimation (DeLASE). Propofol was used to transition animals between the awake state and anesthetized unconsciousness. DeLASE was applied to macaque cortex local field potentials (LFPs). We found that neural dynamics were more unstable in unconsciousness compared to the awake state. Cortical trajectories mirrored predictions from destabilized linear systems. We mimicked the effect of propofol in simulated neural networks by increasing inhibitory tone. This in turn destabilized the networks, as observed in the neural data. Our results suggest that anesthesia disrupts dynamical stability that is required for consciousness.

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Poster

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The Picower Institute for Learning and Memory

Title: Hemifield independence in change localization

Authors: *E. I. BERGER-WOLF[1,2], S. L. BRINCAT[2], H.-B. HAN[2], T. BUSCHMAN[3], E. K. MILLER[2];

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Abstract: Visual working memory has a severely limited capacity—only a small number of items can be held in memory simultaneously. However, capacity is relatively independent in the left and right visual hemifields—even when capacity is saturated in one hemifield, additional items can be encoded into working memory from the opposing hemifield. Here, we show this hemifield independence is also evident in the pattern of choice errors in a change localization task. Two rhesus macaque subjects were shown a brief bilateral display of 2-5 colored squares to encode into working memory and retain over a blank delay. A nearly identical display was then shown with the color of one square (the target item) changed. The task was to saccade to the color-changed target. Overall, the subjects performed well (85% with 2 items to 67% with 5 items), but the errors they did make were distributed non-randomly. They were significantly more likely to select incorrect (unchanged) items in the same (ipsilateral) visual hemifield as the target than in the opposite (contralateral) hemifield. This effect persisted when target-to-choice distance was regressed out, indicating that it was an effect of hemifield per se, rather than overall spatial location. The hemifield choice effect was stronger with greater working memory load—as the number of items in the ipsilateral hemifield increased, the relative probability of choosing an incorrect ipsilateral item increased. However, the effect was present even with identical loads in the two hemifields, suggesting it is distinct from known hemifield effects in working memory encoding/storage. In summary, we have found a novel hemifield independence in the distribution of behavioral change localization errors. This suggests that visual working memory is relatively independent across the left and right hemifield not only in its encoding and storage, but also in how it is read out to produce behavior. Ongoing efforts are directed at comparing alternative models to explain these effects and examining their neural basis in prefrontal and posterior parietal activity.

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Poster

PSTR363: Prefrontal Mechanisms in Non-Human Primates

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Topic: H.04. Executive Functions

Support: NSERC Discovery Grant RGPIN-2023-05079

Title: Repeated within-session intra- and extra-dimensional set shifts in the marmosets

Authors: *M. ALVI[1], R. NATHANIEL[1], K. RAI[2], L. MA[1];
[1]Psychology, York Univ., Toronto, ON, Canada; [2]York Univ., Toronto, ON, Canada

Abstract: Cognitive flexibility is the brain's ability to suppress the current choices or strategies in favor of better alternatives when the context changes. Reductions of cognitive flexibility is a transdiagnostic deficit in several neuropsychiatric disorders. How the primate brain supports this process is not well understood.We trained 4x male marmosets on a novel touchscreen-based Wisconsin Card Sorting Task (WCST), involving 2 dimensions: 3 shapes (star, square, heart) and 3 colours (yellow, red, blue). First, they underwent shape training, in which they must choose the correct one from 2 black shapes to obtain a reward. They were then trained on the remaining 2 shape pairings. Thus, each shape served as either target or foil in different sessions. They received the same training for colours, presented as circular patches. Once learned all colours and shapes as simple stimuli, animals progressed to the full marmoset WCST (mWCST), in which they must first identify and choose the compound stimulus (i.e. colourful shapes) with the target feature (e.g. red), ignoring its other dimension (i.e. shape). Once they reached 80% correct in a 10-trial block, the target feature shifted either within dimension (e.g. blue) or across dimensions (e.g. square). All 4 marmosets quickly learned to perform multiple rule switches (range: 2-9) within a daily session, both intra-dimensionally and extra-dimensionally, within only 3 sessions of training on the full mWCST. Next we will conduct electrophysiological analysis of the neuronal and ensemble correlates for both intra-dimensional and extra-dimensional set shifting in the marmoset brain.

Disclosures: M. Alvi: None. **R. Nathaniel:** None. **K. Rai:** None. **L. Ma:** None.

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Program #/Poster #: PSTR363.10/T1

Topic: H.04. Executive Functions

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Title: Structured representation of a symbolic action grammar across primate frontal cortex

Authors: *L. Y. TIAN[1], K. G. GUPTA[2], J. TENENBAUM[3], X.-J. WANG[4], W. FREIWALD[1];
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Abstract: The ability to generate novel thoughts and actions to solve new problems is a fundamental property of intelligence. This creative capacity has been hypothesized to depend on cognitive operations resembling symbolic grammars, in which abstract representations are systematically combined in a compositional, goal-directed manner. Whether and how symbolic grammars are implemented in structured neural representations remains unclear. Here, we developed an interdisciplinary approach to study the neural implementation of grammar,

centered around a novel drawing task in which macaque monkeys learn and generalize grammars for motor action. We have found that macaques successfully learn and generalize action grammars to draw new images. Behavioral analyses indicate that these grammars consist of a small set of action symbols (e.g., strokes such as circles or lines) and abstract syntactic rules (e.g., “repeat three times”). To investigate neural mechanisms of these action grammars, we recorded simultaneous unit activity across multiple areas of the frontal cortex (sixteen 32-electrode arrays), spanning primary motor, premotor, medial prefrontal, lateral prefrontal, and frontal polar cortices. In ongoing analyses, evidence is emerging of a functional hierarchy across the frontal cortex, with different areas preferentially representing distinct levels of abstraction in an action grammar, including motor primitives, action symbols, and syntactic rules. By combining analyses of neural activity with interrogation of neural network models trained in this drawing task, we are pursuing a mechanistic understanding of how neural dynamics implement cognitive operations consistent with symbol manipulation in an action grammar. Our combination of behavioral, neural, and computational findings suggests that primates represent complex action sequences in terms of their abstract grammatical structure, and that components of this cognitive representation map onto different areas of the frontal cortex.

Disclosures: L.Y. Tian: None. **K.G. Gupta:** None. **X. Wang:** None. **W. Freiwald:** None.

Poster

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Topic: H.04. Executive Functions

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Title: Building Compositional Tasks with Shared Neural Subspaces

Authors: *S. TAFAZOLI[1], F. M. BOUCHACOURT[2], A. ARDALAN[2], N. T. MARKOV[2], M. UCHIMURA[2], M. G. MATTAR[3], N. D. DAW[2], T. J. BUSCHMAN[2];
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Abstract: Cognition is remarkably flexible - we are able to rapidly learn and perform many different tasks. Computational modeling has found that when artificial neural networks are trained to perform multiple tasks, they will re-use representations and computational components across tasks. Yet, it is unknown whether the brain can similarly re-use components across tasks. To address this, we recorded from frontal, parietal, temporal cortices and basal ganglia while monkeys switched between three compositionally-related categorization tasks. In Task S1, the animals categorized a stimulus based on its shape and responded with a saccade to the upper-left or lower-right location. In Task C2, the same stimulus was categorized by its color and the animal indicated their decision with an upper-right or lower-left saccade. In Task C1, the

monkeys categorized by color (as in Task C2) but responded with a saccade to the upper-left or lower-right (as in Task S1). Thus, the three tasks could be thought of combining a categorization sub-task (shape or color) and a response sub-task (upper-left/lower-right or upper-right/lower-left). Neural recordings found task-relevant information was encoded in the activity of neurons in prefrontal cortex. Specifically, there were 'subspaces' within the high-dimensional space of neural activity that represented the shape and color category of the stimulus and the motor response. Consistent with the hypothesis that tasks are compositional, we found the same subspaces were shared across tasks. Task C1 and Task C2 used the same subspace of neural activity to represent the color category of the stimulus, and Task C1 and Task S1 used the same subspace to represent the upper-left/lower-right motor response. In this way, Task C1 could be composed of the sequential engagement of the color categorization subspace (shared with Task C2) and the left/right response subspace (shared with Task S1). The shared representations were dynamically recruited as the monkeys switched between tasks: neural representations in the relevant shared sensory subspace were transformed to the relevant shared motor subspace based on the task in effect (i.e. shared color subspace was transformed to upper-left/lower-right or upper-right/lower-left response in Task C1 or C2, respectively). The engagement of subspaces was flexible: as monkeys discovered the task in effect, their internal belief about the current task predicted the strength of representations in task-relevant subspaces. In sum, our findings suggest that the brain can flexibly perform multiple tasks by compositionally combining task-relevant neural representations across tasks.

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Poster

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Topic: H.04. Executive Functions

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Title: Drift-diffusion models pinpoint neurocomputational failure in the NMDAR primate model of prefrontal dysfunction in schizophrenia

Authors: *D. WANG[1], D. A. CROWE[2], O. L. CALVIN[3], R. K. BLACKMAN[4], A. L. DENICOLA[5], S. M. BRUNSON[6], M. V. CHAFEE[7];
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Abstract: Schizophrenia is thought to result in part from malfunction of NMDA receptor (NMDAR) mediated synaptic transmission, causing computational failure in prefrontal networks, leading to deficits in cognitive control. To elucidate the neural malfunction underlying cognitive control impairment, we administered an NMDAR antagonist to monkeys performing a cognitive control task (DPX) that measures specific deficits in the disease. In the DPX task, the response required to a probe stimulus is contingent on a preceding cue, requiring cognitive control. We previously demonstrated that administration of NMDAR antagonists to monkeys induces a specific error pattern strongly resembling the errors made by people with schizophrenia. Subjects of both species commit increased errors disproportionately on the subset of trials in which a contextual cue stored in working memory instructs monkeys to override a prepotent response to the subsequence probe. This suggests that NMDAR antagonism in monkeys mimics certain aspects of the disease state in humans.To quantify the computations underlying task performance, and relate the computations to neural dynamics observed during task performance, we fit drift-diffusion models to behavioral choice and response time distributions in four monkeys. We found that DDMs fit to subsets of trials with different cue-probe combinations accurately modeled choice and response time distributions in the control condition, and that blocking NMDAR reduced drift rate and increased nondecision time parameters in the model fits. These two changes in computational parameters resemble those found in people with schizophrenia performing the same task. To identify the changes in neural function driving these computational changes, we decoded the cue-defined state from activity of neural ensembles in prefrontal cortex on a trial-by-trial basis, and entered the neural data as an explanatory variable in the DDM models. We found that (1) single trial decoding accuracy significantly influenced the drift rate parameter in the DDM fits to behavioral choice data, (2) blocking NMDAR significantly reduced contextual cue decoding accuracy, and (3) weakened the influence of contextual cue decoding on drift rate. Neural signals encoding the imperative probe were not affected. These results suggest that computations for cognitive control are well captured by drift-diffusion models, that the underlying drift-diffusion process integrates information about context held in a working memory buffer, and that computational errors in schizophrenia reflect a disruption of the drift process downstream of NMDAR malfunction in the disease.

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Poster

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Topic: H.04. Executive Functions

Title: Understanding compositional generalization in the brain with a vector addition task

Authors: *C. TANG[1], M. JAZAYERI[2];
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Abstract: We trained two monkeys on a task involving compositionality and recorded neural activity in the dorsomedial frontal cortex (DMFC). Specifically, monkeys had to compute the endpoint of a displacement (target) on a 2D display by combining information about its starting point (start) with information about the displacement's magnitude and direction (vector). On each trial, while fixating a central spot, monkeys were presented with a circle indicating the start as well as a flow field around the fixation point indicating the vector. The monkeys had to make a saccade to the target to get the reward. To study compositional generalization, the experiment was divided into two stages. In the first training stage, animals were presented with a subset of possible combinations of start and vector (training set). After learning to perform the task with the training set, we confronted animals with novel held-out combinations (test set). Using various behavioral measurements and performance metrics we established that animals were able to make correct compositional generalizations in some conditions while failing to correctly generalize in others. In cases where the animal succeeded, the monkeys' choices were closer to the target than expected from a memorization strategy using a lookup table of conditions in the training set. In cases where the animal failed, the behavior was better explained by the lookup table model. Next, we used Neuropixles to record densely from DMFC neurons while animals performed the task. Currently, we are analyzing the structure and dynamics of neural activity associated with compositional generalization. A key focus in the forthcoming analyses is to leverage the partial generalization observed in behavior and contrast neural data in the success and failure conditions to understand the key computational criteria that enable compositional generalization. We expect the brain to solve the task by establishing a high-dimensional neural manifold with a 2D embedding mimicking the task structure, and hypothesize that the degree of generalization would depend critically on the structure of neural trajectories determined by the flow field over this manifold. We expect failures to reflect distortions and biases of the flow field due to idiosyncrasies of learning in the two animals. This work holds promise to advance our understanding of how the primate brain organizes knowledge in ways that could support compositional generalization.

Disclosures: C. Tang: None. **M. Jazayeri:** None.

Poster

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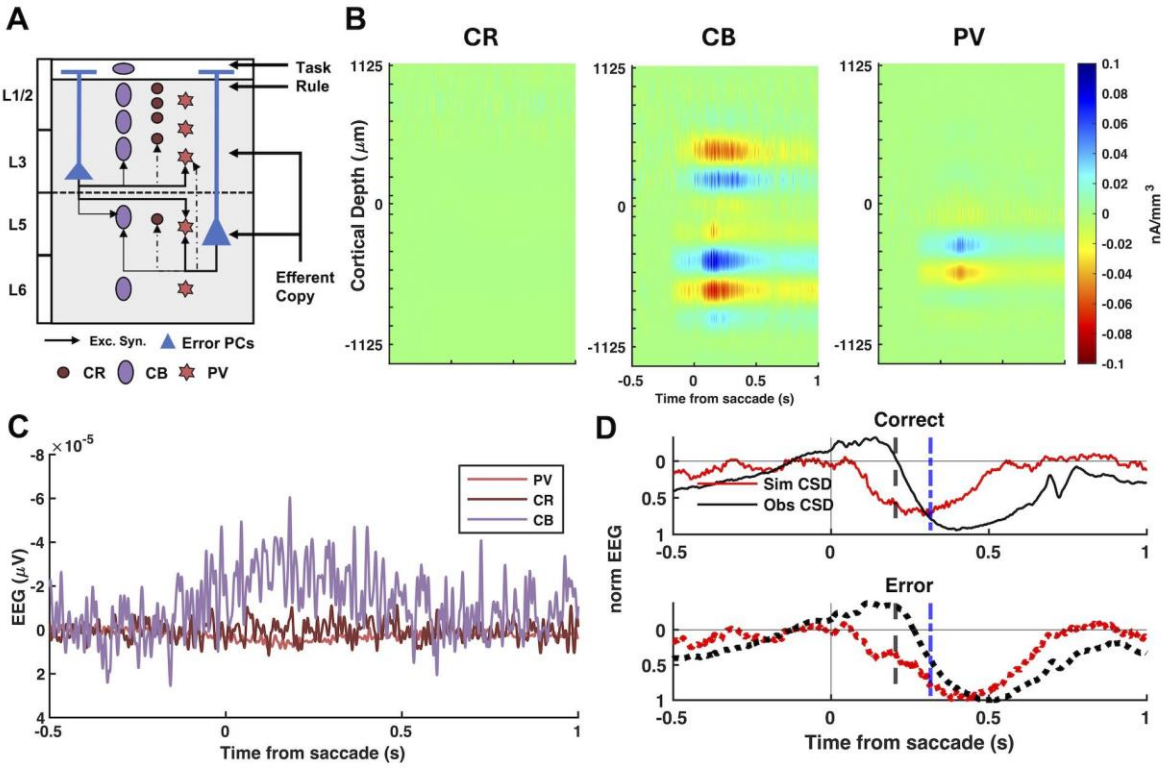
Title: Multiscale electrical signatures of interneurons in agranular frontal cortex of macaques during performance monitoring

Authors: *B. HERRERA[1], A. SAJAD[2], S. P. ERRINGTON[3], J. D. SCHALL[4], J. J. RIERA[5]; [1]Florida Intl. Univ., Miami, FL; [2]Psychology, Vanderbilt Univ., Nashville, TN; [3]Psychology, Washington Univ. Sch. of Med., Saint Louis, MO; [4]Biol., York Univ., Toronto, ON, Canada; [5]Biomed. Engin., Florida Intl. Univ., Miami, FL

Abstract: The source of the EEG error-related negativity (ERN) and associated post-error positivity (Pe) is uncertain. Most biophysical modeling studies have focused on evaluating the local field potentials (LFPs) with associated current source density (CSD) and derived EEG signatures exclusively in terms of distinct pyramidal cell (PC) populations. The few studies examining the contribution of GABAergic interneurons have focused mainly on spiny stellate and basket cells, used a limited number of morphological reconstructions, did not account for differences in interneuron density across cortical layers, and did not incorporate the modulation of local synaptic inputs from PCs observed in relation to a specific behavior. In this study, we evaluated the contribution of GABAergic interneurons in the agranular frontal cortex of macaque monkeys to the LFPs/CSD and EEG during a countermanding (stop signal) task. Distinguishing calbindin (CB), calretinin (CR), and parvalbumin (PV) interneurons based on calcium-binding proteins, we used 54 detailed biophysical models of interneurons with distinct morphological reconstructions, simulated with the observed densities across cortical layers and reconstructed synaptic inputs from PCs. Background inputs to simulated interneurons were constrained by neurophysiological observations from two macaque monkeys performing a countermanding (stop signal) task. We found that CB and PV populations have a nonnegligible contribution to the LFP/CSD and EEG. CR interneurons only contribute to the signal as white noise. We also found that the ERN and Pe were accounted for better by combined rather than separate contributions of error-related PCs and CB with PV interneurons. This work reveals an unexpected nonnegligible contribution of interneurons to an EEG event-related potential.



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Poster

PSTR363: Prefrontal Mechanisms in Non-Human Primates

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Title: The frontopolar cortex of a macaque monkey monitors one's own decision in exploring implicit option values

Authors: *T. HASEGAWA, K. MIYAMOTO;
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Abstract: The frontopolar cortex (FPC), the most anterior portion of the prefrontal cortex, is found only in primates and believed to be involved in high-order cognitive functions. Previous imaging and lesion studies suggest that the FPC is involved in the metacognitive perception of uncertainty, reorientation of cognitive resources, and explorative decision making. However, due to the difficulty in accessing the FPC in non-human primates, knowledge of FPC activity at the

single-cell level is limited. Here, we designed a customized head-fixation device and recording chamber to enable the single unit recordings from the FPC of macaque monkeys at the awake state. We trained one male rhesus monkey (*Macaca mulatta*) to perform a multi-armed bandit task consisting of two types of blocks: with or without the feedback for correct option, which provides the counterfactual choice in failed trials (i.e., unchosen correct choice). Consistent with previous studies, many FPC neurons show firing rate modulation at the time of outcome feedback (i.e., correct or incorrect). Among the feedback-modulated neurons, most of them (89%; 8/9 neurons) changed their firing rates only if the feedback for correct option is absent. These results suggest that the FPC neurons monitor and/or evaluate one's own decision only during exploring implicit option values.

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Poster

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Title: Decoding prefrontal cortex dynamics: unveiling information processing with Neuropixel recordings

Authors: *E. MEYERS[1], F. BAIG[2], W. DANG[3], J. ZHU[4], Z. WANG[5], A. MACHADO[5], B. HAMMOND[5], C. CONSTANTINIDIS[4];
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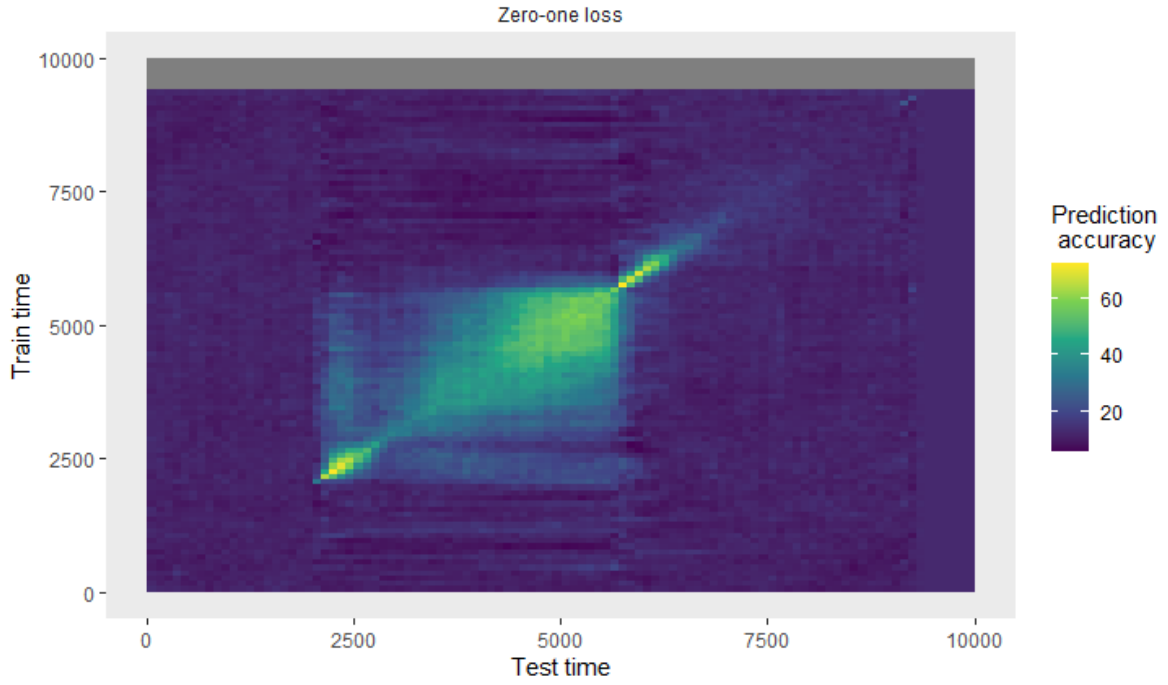
Abstract: Neuropixel probes offer the potential for breakthroughs in understanding neural information processing due to their ability to simultaneously record from large populations of neurons. In this study, we used these probes to record from the prefrontal cortex (PFC) across multiple sessions as monkeys engaged in a delayed ocular motor response (ODR) task. To analyze the data, we used classical single neuron analyses along with neural population decoding analyses. Our decoding results showed the characteristic pattern of information flow seen in ODR tasks, with dynamic neural activity patterns occurring during stimulus onset and while the monkeys were making saccades, and a stable code with ramping information content during the delay period. Additionally, a comparative analysis between single-unit activity (SUA) and multi-unit activity (MUA) demonstrated that both types of units had the similar amount of information on a per unit basis, however, because SUA allowed us to split the data from each recording

session into many more units, overall SUA carried much more information. We also found high variability across recording sessions, with some sessions exhibiting much higher information content than others with comparable neuron numbers, depending on recording site. Finally, our investigation into simultaneous versus pseudo-populations revealed similar levels of information, and we saw that with the approximately ~200 units recorded simultaneously in each session, the data was still too noisy to make accurate single trial predictions. These insights deepen our understanding of PFC function and offer valuable guidance for optimizing experimental designs that utilize Neuropixel probes.



Disclosures: E. Meyers: None. **F. Baig:** None. **W. Dang:** None. **J. Zhu:** None. **Z. Wang:** None. **A. Machado:** None. **B. Hammond:** None. **C. Constantinidis:** None.

Poster

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Ontario Graduate Scholarship

Title: Functional architecture of visual responses in dorsal and ventral banks of cingulate cortex

Authors: *P. THIRUNAVUKKARASU[1], S. P. ERRINGTON[2], A. SAJAD[3], J. D. SCHALL[1]; [1]York Univ., Toronto, ON, Canada; [2]Washington Univ. Sch. of Med., Saint Louis, MO; [3]Vanderbilt Univ., Nashville, TN

Abstract: Primate survival depends on decision-making and control of actions guided by consequences. This ability is referred to as cognitive control. Effective cognitive control requires a machinery that monitors performance and reward to alter the parameters governing behavior to improve outcomes. Previous research in humans, macaques, and rodents has demonstrated a role of the medial frontal cortex (supplementary eye field and cingulate cortex) in detecting errors, resolving conflict, registering success, and exerting pro-active control on saccade production. The cortical circuitry accomplishing these computations has not been fully resolved. Here, we analyze neural spiking data from two monkeys (*Macaca mulatta*) collected using linear electrode arrays to describe the visual properties of neurons across cortical layers in the dorsal and ventral banks of the caudal segments of anterior cingulate cortex (actually midcingulate cortex, MCC) during a visually guided saccade countermanding task. Monkeys were rewarded for shifting gaze to a visual target unless, in infrequent random trials a stop signal appeared, which instructed the subject to cancel saccade initiation. After sampling over 1500 neurons in MCC, ~10% demonstrated significant modulation in response to a visual target. Typically, these responses were sustained, discharging until after saccade production. The majority of visually responsive neurons were most sensitive to a visual target appearing in one hemifield. Interestingly, as observed previously in SEF, MCC visual neurons showed an unexpected preference for ipsilateral visual stimuli. Certain neurons also exhibited anticipatory pre-target ramping. MCC visual neurons were modulated significantly later than those in occipital and temporal visual areas, as well as other frontal regions such as frontal and supplementary eye fields. We additionally report laminar differences between the task-related laminar visual response between the dorsal and ventral banks of MCC. These findings provide the first report of the functional architecture of visual signals in two discrete regions of cingulate cortex and provide important constraints for microcircuit models of these areas.

Disclosures: P. Thirunavukkarasu: None. **S.P. Errington:** None. **A. Sajad:** None. **J.D. Schall:** None.

Poster

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Topic: H.04. Executive Functions

Support: NIH/NIA Grant R01AG068168-01

Title: Effects of mesenchymal stromal cell-derived extracellular vesicles on prefrontal cortical pyramidal neurons and executive function in aging

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Abstract: Age-related declines in cognition can occur as early as middle age in some proportion of humans and rhesus monkeys with the earliest deficits seen in executive function (EF), a cognitive domain mediated by the prefrontal cortex (PFC). The PFC displays early age-related increases in inflammation and changes in neuronal properties such as hyperexcitability and reduced spine density. While there are currently no treatments for reversing these changes, mesenchymal stromal cell-derived extracellular vesicles (MSC-EVs), with their anti-inflammatory properties and capacity to reduce neuronal excitotoxicity, present a potential therapeutic. In this study, we assessed the efficacy of MSC-EVs to ameliorate age-related cognitive impairment and biophysical and morphological changes in pyramidal neurons in the PFC areas underlying EF - the lateral PFC area 46 (LPFC) and the medial PFC/anterior cingulate area 24/32 (ACC) of normally aging monkeys. Late middle-aged monkeys (*M. mulatta*; n=1 F and 2 M vehicle; n=2 F and 1 M EV-treated; 20.2-26.8 y.o.) underwent baseline cognitive testing before receiving 18 months of biweekly treatment (EVs or vehicle) and then re-tested post-treatment. Overall, EV-treated monkeys performed significantly better on the post-treatment Delayed Recognition Span Task (DRST), a spatial working memory test, in contrast to the control group ($p<0.01$). After completion of cognitive tests, acute brain slices were harvested for *in vitro* whole-cell patch clamp recording and intracellular filling to assess biophysical and morphological properties of layer 3 pyramidal neurons in LPFC and ACC. Two-way ANOVA (area x group) of electrophysiological data revealed significant EV-mediated increases in excitability of neurons in both areas, manifested by higher input resistance (Rn) (LPFC $p<.001$, ACC $p<.001$), faster single action potential properties (duration, rise, and fall: $p<.05$ in both areas), decreased rheobase (LPFC $p<.05$) and increased firing frequency (LPFC $p<.05$). LPFC Rn and rheobase were significantly correlated with DRST change from baseline (DRST vs. Rn, $r= .844$, $p<.05$; DRST vs. rheobase $r= -.843$, $p<.05$). Whole-neuron reconstructions showed that EV treatment resulted in more basal junctions in ACC ($p<.05$) but not LPFC neurons, which implies an area-specific increase in dendritic complexity. These single-neuron differences may affect local and long-range network activities that support EF, which can be assessed in future studies. Overall, we demonstrate the therapeutic potential of MSC-EVs to improve cognitive function and alter PFC neuronal properties.

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Poster

PSTR363: Prefrontal Mechanisms in Non-Human Primates

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Topic: H.04. Executive Functions

Support: R01 MH116008
RF1 AG06283

Title: Distribution and properties of lateral prefrontal area 9 connections in anterior cingulate cortex of rhesus monkeys

Authors: *Y. ZHOU[1], M. HSIUNG[2], C. A. MOJICA[1], T. L. MOORE[1], D. L. ROSENE[1], J. I. LUEBKE[1], M. MEDALLA[1];
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Abstract: As part of the prefrontal executive network and limbic system, the anterior cingulate cortex (ACC) regulates cognitive processing for decision-making through its connections with the lateral prefrontal cortex (LPFC). The ACC is found to have three anatomically and functionally distinct subregions—rostral ACC area 32 (A32), dorsal ACC area 24 (A24a-c), and ventral subcallosal ACC area 25 (A25), which have been shown to connect with limbic structures such as the amygdala (AMY) and entorhinal cortex, and motor regions such as dorsal premotor cortex, in different extent. However, the precise laminar organization and physiological properties of LPFC connections, in terms of its inputs to or outputs from ACC have not been elucidated. In this study, we injected a combination of retrograde and anterograde tracers into LPFC area 9 (A9) to quantify the distribution of labeled projection neurons from (outputs) and axon terminals to (inputs) the ACC subregions of adult rhesus monkeys of both sexes (*Macaca mulatta*; n=3; 6-13 years old; 1 female, 2 males). A24a and A24b, but not A24c, showed the greatest relative density of retrograde-labeled projection neurons (ACC->A9) and anterograde-labeled terminals (A9->ACC), as compared to A25 and A32 ($p<0.05$) in both layers 2-3 (L2-3) and 5-6 (L5-6). Among all the subregions and laminar groups, A24a layer 1 has the greatest relative density of labeled terminals ($p<0.05$). In addition, using *in-vitro* whole-cell patch clamp recording, we assessed biophysical signaling properties of tracer-labeled ACC->A9 projection neurons in dorsal ACC (A24) L3 and compared the results to our previous dataset of ACC->AMY projection neurons. We found that L3 ACC->A9 projection neurons exhibited lower input resistance (Rn), indicating lower excitability, than ACC->AMY neurons ($p<0.05$). Voltage clamp recordings (V_{hold} = -40mV) revealed that ACC->A9 neurons had longer rise time of inhibitory postsynaptic currents (IPSCs) as compared to ACC->AMY neurons ($p<0.05$), while no differences found in spontaneous excitatory postsynaptic currents (EPSCs) properties. Our results highlighted dorsal ACC, specifically A24a and b, as an important subregion for processing cognitive information by both sending outputs to and receiving inputs from LPFC A9 and that these projections have pathway-specific biophysical properties. These findings are fundamental to the understanding of information integration within ACC for LPFC-ACC-AMY network interactions that are crucial for cognitive-emotional integration and decision making.

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Poster

PSTR363: Prefrontal Mechanisms in Non-Human Primates

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Topic: H.04. Executive Functions

Support: NIH/NIMH R01MH116008
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Title: Regional and Pathway-Specific Distribution of Cannabinoid CB1 and Dopamine D2 Neuromodulatory Receptors in Primate Anterior Cingulate Cortex

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Abstract: Neuromodulation of the anterior cingulate cortex (ACC) through interaction of various ascending neurotransmitter-specific systems is thought to be important for cognitive-emotional regulation. These functions are also dependent on the pathways interconnecting distinct rostral (area 32), dorsal (area 24), and ventral (area 25) ACC subregions with diverse cortico-limbic structures such as the lateral prefrontal cortex (LPFC), a key area for cognition, and the amygdala (AMY), the center for emotional expression. How different neurotransmitter specific signals interact with these cortico-limbic circuits in the ACC is largely unknown in the primate brain and likely depend on layer and pathway-specific expression of distinct neuromodulatory receptors. Here, we investigate the expression of receptor subtypes involved in endocannabinoids and dopamine signaling, which are key neuromodulators of the cortico-limbic system and implicated in stress. The cannabinoid 1 receptor (CB1R) and dopamine receptor 2 (D2R) are inhibitory G-protein coupled receptors that are mainly located on presynaptic terminals to inhibit neurotransmitter release. Further, it is known that these receptors functionally interact, but their co-expression in diverse cortico-limbic circuits in the primate brain are largely unknown. Thus, we examined the expression of these receptors on distinct ACC subregions, layers and pathways using tract-tracing and immunohistochemistry. Bidirectional tract tracers were injected into LPFC area 9 (A9) or AMY in rhesus monkeys (*Macaca mulatta*; n=4; 6-13 years old; 2 female, 2 males) to label projection neurons (outputs) and axon terminals (inputs) in ACC, and assess their co-expression with CB1R and D2R. We found greater densities (% area label) of CB1R in upper compared to deep layers of A25 ($p < 0.05$), while D2R was more uniformly expressed across areas and layers of the ACC. However, analyses of pathway-specific expression showed diversity in D2R+ A9 vs AMY projection neurons across ACC subregions. In the upper layers, the density of D2R+ A9 projection neurons ($p < 0.01$) is the lowest in A24c; The deep layers showed the opposite pattern, with A24c having the highest density of D2R+ A9 projection neurons ($p < 0.01$). A32 had the lowest density of D2R+ AMY projection neurons in the deep layers across ACC subregions ($p < 0.01$). Our results suggest differential cannabinoid and dopaminergic neuromodulation and interaction within distinct ACC subregions and cortico-

limbic pathways, which maybe implicated in the neurochemical imbalance of cortico-limbic networks in stress and affective disorders.

Disclosures: M. Hsiung: None. **Y. Zhou:** None. **M. Medalla:** None.

Poster

PSTR364: Prefrontal Mechanisms in Non-Primate Mammals

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Topic: H.04. Executive Functions

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NINDS Grant NS105602

Title: Neurochemical and circuit heterogeneity of cognition-modulating prefrontal corticotropin-releasing factor (CRF) neurons

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Abstract: Prefrontal cortex (PFC)-dependent cognitive dysfunction is associated with multiple psychiatric disorders. Treatment of this dysfunction is hindered by our limited understanding of the neurobiology underlying PFC-dependent cognition. In prior immunohistochemical and recently completed *in situ* hybridization studies we have observed a surprisingly rich population of CRF neurons in the medial PFC of rats. Subsequent chemogenetic studies demonstrated that CRF neuronal activity in the caudal dorsomedial PFC (dmPFC) of rats impairs both working memory and sustained attention. Interestingly, while the working memory actions of PFC CRF neurons were dependent on local CRF receptors, this was not the case for sustained attention. These results suggest the potential for subpopulations of cognition regulating CRF neurons, including both GABAergic interneurons and glutamatergic projection neurons. In double labeling studies in male and female rats, we observed that approximately 85% of CRF neurons were glutamatergic (CRF_{Glu}) while the remaining 15% were GABAergic (CRF_{GABA}). In recently completed studies we used an intersectional viral approach to examine the working memory and sustained attention effects of chemogenetic activation of these neuronal subpopulations in males and females. Given earlier observations, all testing of females was done outside of proestrus. We observed that activation of CRF_{GABA} neurons impaired working memory but not sustained attention. In contrast, activation of CRF_{Glu} neurons impaired both working memory and sustained attention. There were no sex differences in the actions of CRF_{GABA} and CRF_{Glu} neurons. Interestingly, the working memory impairing effects of caudal dmPFC CRF_{GABA} neurons were not dependent on local CRF receptors, while those of CRF_{Glu} neurons were. Combined with previous observations, these results suggest complexity in the neurocircuitry underlying the cognitive actions of PFC CRF_{GABA} and CRF_{Glu} neurons. Specifically, CRF_{GABA} neurons

influence working memory, but not sustained attention, and these actions involve projections outside the caudal dmPFC. In contrast, CRF_{Glu} neurons impact working memory, at least in part, via local projections while the sustained attention effects (and potentially working memory) involve distal projections. In recent studies we observed that caudal dmPFC CRF neurons provide a remarkably dense innervation of the lateral mediodorsal thalamus. Ongoing studies are testing the hypothesis that caudal dmPFC CRF_{GABA} and CRF_{Glu} neurons impact cognition via CRF action in this region.

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Poster

PSTR364: Prefrontal Mechanisms in Non-Primate Mammals

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Topic: H.04. Executive Functions

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NARSAD Young Investigator Award

Title: A cortical locus for modulation of arousal states

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Abstract: Fluctuations in arousal are key determinants of spontaneous cortical activity and function. Several subcortical structures, including neuromodulatory nuclei, are involved in the regulation of arousal. However, much less is known about the role of cortical circuits that provide top-down inputs to arousal-related subcortical structures. Here, we investigate the role of a major subdivision of the prefrontal cortex, the anterior cingulate cortex (ACC), in arousal modulation. Pupil size, heart rate, facial movements, and locomotion were used as non-invasive measures of arousal and behavioral state. Fiber photometry recordings showed a strong association between ACC activity and spontaneously occurring pupil dilations/face movements independently of locomotion. Machine vision assisted, closed loop optogenetic ACC inactivation suppressed ongoing pupil dilations, suggesting that the ACC modulates global arousal responses. Conversely, optogenetic ACC activation increased arousal independently of locomotion. In addition to modulating global arousal, ACC responses to salient sensory stimuli scaled with the size of evoked pupil dilations. Consistent with a role in modulation of evoked arousal responses, sensory-evoked pupil dilations were suppressed with ACC inactivation. Comparing arousal-related ACC and LC activity suggested that LC activity triggers transient increases in arousal

while ACC activity plays a role in sustaining these events. Collectively, our experiments identify the ACC as a key site for arousal modulation and provide the foundation for understanding cortical-subcortical interactions regulating arousal states.

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Poster

PSTR364: Prefrontal Mechanisms in Non-Primate Mammals

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Topic: H.04. Executive Functions

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HKRGC-GRF 14115821
CityU SGP Grant 9380157

Title: A novel behavior paradigm for investigating cognitive flexibility in rodents

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Abstract: Executing multiple tasks simultaneously, commonly seen in daily lives such as talking while walking, is a manifestation of the flexibility of our cognitive functions. However, humans have limited ability in performing such tasks, which is often exacerbated in a variety of neurological diseases. Deciphering the mechanism underlying this type of cognitive flexibility in human has been hampered by the poor spatiotemporal resolution of neuroimaging methods. To facilitate in-depth investigation of their neural underpinning using animal model, we developed a novel behavioral paradigm in mouse. Mice were trained in a task combining a cognitive and a motor task mimicking distracted car-driving. In this paradigm, the animals learned to manipulate a lever (like operating the steering wheel) during which they needed to discriminate between two auditory cues in a go/nogo test (i.e., cognitive decision-making). We observed interference in both cognitive and motor aspects in the early stage of training and to different extents, analogous to those observed in human and primate studies. Yet some animals were able to partially restore their performance with sufficient training. This paradigm therefore would allow the study of the neural mechanism underlying this type of cognitive flexibility via interventional manipulation.

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Poster

PSTR364: Prefrontal Mechanisms in Non-Primate Mammals

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Program #/Poster #: PSTR364.04/U3

Topic: H.04. Executive Functions

Support: NINDS/NIA R01NS129711

Title: Investigating medial prefrontal cortex activity during a novel behavioral task

Authors: *J. E. RYSTED[1], Y. KIM[1], M. A. WEBER[1], K. GUPTA[2], P. J. BOSCH[1], R. DEAN[3], G. M. ALDRIDGE[1];
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Abstract: The medial prefrontal cortex (mPFC) plays a crucial role in mammalian executive function, including cognitive flexibility, goal directed behavior, and timing. Executive function processes correlate with low frequency theta oscillations in the mPFC; however, it is unknown which cells drive these oscillations. We hypothesize that layer 5 neuron activity in the mPFC significantly correlates with the theta oscillations observed during executive function tasks. In order to investigate mPFC activity in mice we utilized simultaneous 2-photon calcium imaging and extracellular electrophysiology during a novel head-fixed behavioral task (**S**elect side **T**o **O**btain **P**rize (STOP) task). Here, we injected GCaMP7f into the mPFC of adult mice and subsequently implanted an optical prism, extracellular electrode, and magnetic head bar in order to record *in vivo* mPFC activity during the STOP task. During this task, mice are head-fixed and trained to run on a floating platform with two separate "pause" target zones associated with a tone. Each trial lasts 2 minutes and mice are rewarded when they correctly pause on one of the two target zones for 3 seconds. Rewarded target zones are predetermined pseudo-randomly on a trial-by-trial basis, thus requiring a behavioral correction if the wrong target zone is chosen during the trial. mPFC activity is simultaneously recorded via 2-photon calcium imaging and local field potential electrophysiology. Our preliminary data show distinct reward-related activity in the mPFC during the STOP task relative to non-goal directed behavior outside of the trial. Moreover, this reward-related activity results in low frequency theta oscillations and neuronal ensemble activity also distinct from non-goal behavior, thus suggesting a shift in network activity when goal-oriented behavior is engaged. Ongoing experiments are aimed at applying these methods to mouse models of Lewy Body Disease with Dementia (DLB) to examine the impact of α-synuclein overexpression on mPFC activity during cognitive flexibility and timing.

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Poster

PSTR364: Prefrontal Mechanisms in Non-Primate Mammals

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Program #/Poster #: PSTR364.05/U4

Topic: H.04. Executive Functions

Title: Medial prefrontal projections in interval timing

Authors: *X. DING[1], M. A. WEBER[1], T. BUTLER[4], A. BOVA[1], S. GUERRERO[2], J. RESCH[3], N. S. NARAYANAN[5];
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Abstract: Abstract Interval timing is a cognitive control process of tracking the passage of time over seconds-to-minutes and is impaired in patients with neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Our lab has shown that neurons in both the rodent medial prefrontal cortex (mPFC) and the dorsomedial striatum (DMS) display patterns of ramping activity - or monotonic changes in firing rate – during a timed interval. In this study, we aimed to study interval timing related patterns of activity in two specific mPFC projections in rodent: mPFC to DMS and mPFC to mediodorsal thalamus (MD). To investigate these projections, we used 1) fiber photometry to record calcium dynamics in neuronal cell bodies of each projection; 2) optogenetics to inhibit each projection; 3) single RNA sequence to investigate the molecular profile of each projection. We found that calcium dynamics in mPFC-DMS neurons differ from mPFC--MD neurons during interval timing. mPFC--DMS neurons were modulated during the interval, while mPFC--MD neurons displayed a strong positive reward-related signal. Preliminary data also suggest that optogenetic inhibition of these projections differentially affects interval timing behavior; mPFC--DMS inhibition increases switch response times while mPFC--MD inhibition does not. In addition, we did observe that different mPFC projections have distinct gene expression. Together, these findings inform the function of mPFC projections during interval timing and could enhance our understanding of the pathological mechanisms of cognitive dysfunction.

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Poster

PSTR364: Prefrontal Mechanisms in Non-Primate Mammals

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Topic: H.04. Executive Functions

Support: CA285183
CA224672

Title: Vortioxetine rescues cognitive deficits resulting from prostate cancer treatment via androgen deprivation therapy

Authors: *S. E. BULIN[1,2], B. W. LATIMER[1], K. TAPIA[3], D. A. MORILAK[4];
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Abstract: Androgen Deprivation Therapy (ADT) is a common treatment for prostate cancer. One unfortunate side effect in patients treated with ADT is cognitive impairment. ADT alone has been shown to produce cognitive deficits in visuospatial memory and cognitive flexibility. Using a Copenhagen Rat prostate tumor model, we tested the cognitive effects of ADT in subjects with androgen-sensitive prostate cancer, and tested treatment of the cognitive impairment with vortioxetine (VTX). Using this model, we were able to explore a translationally relevant relationship between prostate cancer and ADT on cognition, as well as a potentially translatable treatment. Copenhagen rats were implanted in the flank with syngeneic androgen-sensitive prostate tumors. After tumors reached criteria of 1 cm^3, rats were treated with 3 mg/kg of Degarelix (GnRH antagonist) or vehicle and provided with 21 days of VTX diet (24 mg/kg/day) or control. Rats were then assessed for changes in visuospatial memory (Novel Object Location; NOL) and cognitive flexibility (Attentional Set-shifting; AST). Preliminary NOL data suggests that compared to Sham/Veh controls, both the presence of tumor alone and DGX treatment alone resulted in a loss of preference for the novel location, suggesting deficits in hippocampal function (n=4-10/group). VTX treatment had no effect in the tumor alone group, but preference for the novel object location was restored in Tum+/DGX+ animals given VTX diet. Preliminary results in AST also suggest that the presence of tumor alone or DGX both resulted in deficits in the set-shifting task. Again, VTX treatment did not rescue deficits in animals with untreated tumors, but Tum+/DGX+/VTX+ were similar to controls (n=6-10/group). This suggests that cancer-related cognitive deficits and ADT-induced deficits act through separate mechanisms, with VTX treatment being effective against ADT-related deficits. Ongoing experiments are currently exploring the mechanism of ADT effects on cognition and the mechanism by which VTX reverses cognitive deficits induced by ADT. These results may inform new treatments for cognitive decline caused by prostate cancer treatment while preserving the tumor-suppressing effect of androgen deprivation therapy.

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Poster

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Topic: H.04. Executive Functions

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Title: Contributions of ovarian hormones to executive functioning in aged female Fischer 344 X Brown Norway F1 hybrid rats

Authors: *K. M. GONZALEZ[1,2], B. SETLOW[3,4], J. L. BIZON[1,4];
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Abstract: Prefrontal cortex (PFC)-mediated executive functions have been shown to change with age, and some studies suggest that sex differences may be present due to altered gonadal hormone levels, mainly driven by menopause. While age-related changes in executive functioning have been successfully modeled in rats, these studies have largely been limited to males. Recent work from our labs evaluated both male and female young adult and aged Fischer 344 x Brown Norway F1 hybrid (FBN) rats in a battery of executive functioning tasks, and found that, in contrast to aged males, which were impaired relative to their young male counterparts, performance in aged females was largely intact. Unlike humans, however, aged female rats maintain estrous cyclicity well into advanced ages. As such, we evaluated whether estrous cycling contributes to maintained performance in aged female rats on intertemporal choice, working memory, and probabilistic reversal learning tasks, on all of which aged males have been shown previously to be impaired. Aged female rats (21 months at the start of testing) underwent either ovariectomy (OVX), in which the ovaries are surgically removed to induce estropause, or control (Sham) surgeries, followed by behavioral testing. In the intertemporal choice task, rats selected between a small, immediately available food reward and a large, delayed food reward delivered after a variable delay period (0-60s). OVX and Sham females did not exhibit behavioral differences, with both groups discounting the large, delayed reward to the same degree. In the working memory task, rats had to recall the location of a lever following a variable delay period (0-24s). Both Sham and OVX groups performed less accurately at longer retention delays, but the two groups did not differ from each other. In the probabilistic reversal learning task that assessed cognitive flexibility, rats had to learn to discriminate between two levers that were reinforced at different probabilities, and which were then switched multiple times per test session. There was no difference in the number of reversals completed across test sessions between OVX and Sham rats. Collectively, these data suggest that maintenance of ovarian hormones in aged female FBN rats does not account for their relative sparing of executive functions compared to aged male rats of the same strain.

Disclosures: K.M. Gonzalez: None. **B. Setlow:** None. **J.L. Bizon:** None.

Poster

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Support: Wellcome Trust 217211/Z/19/Z
Wellcome Trust 224121/Z/21/Z
Wellcome Trust 219627/Z/19/Z
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Title: Frontal cortex clamps behavioural states in basal ganglia during decision-making

Authors: *M. LOHSE[1], B. GONZALES[1], M. SKRETOWSKA[2], A. KHILKEVICH[1], H. DAVIES[1], P. WINDMILL[1], R. CAMPBELL[1], T. D. MRSIC-FLOGEL[1];
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Abstract: Frontal cortex encodes task rules and current goals to allow cognitive control of behaviour. However, the mechanism by which frontal cortex controls brain regions that select and generate behavioural responses is unclear. The basal ganglia are important for learned action selection and densely interconnected with frontal cortex. Frontal cortex may therefore implement cognitive control of learned behaviour via cortico-striatal networks to select appropriate behavioural responses while suppressing inappropriate ones. We investigate this possibility using a multi-demand task that requires sustained periods of impulsivity control while continuously evaluating noisy sensory evidence to determine when to act, and record and manipulate activity in cortico-striatal circuits.We show that control of impulsivity and sensorimotor transformation are controlled by distinct subregions of the frontal cortex. The anterior secondary motor cortex (aMOs) allows translation of sensory evidence into action while postero-central MOs (pcMOs) controls the inhibition of impulsive action. We reveal that aMOs implements task-appropriate sensorimotor mapping through control of neural population dynamics in striatum. aMOs clamps the baseline activity of neurons encoding sensory evidence to establish a task-engaged sensorimotor state. Task state established by aMOs is encoded in a population dimension orthogonal to evidence accumulation. This positions task relevant evidence in a neural state capable of influencing action while the animal is engaged in the task. Concurrent impulsivity control, allowing animals to wait long enough to see a rewarding change, is established by a parallel cortico-striatal network. This network is causally dependent on indirect pathway neurons in dorso-medial striatum (DMS) - the striatal area receiving densest inputs from pcMOs. There, pcMOs enables DMS to generate counter-action activity during early stages of preparatory activity, thus suppressing the probability of impulsive action. Our results delineate how parallel frontal-striatal networks balance multiple action determinants through distinct state control mechanisms to generate appropriate behaviour at the right time.

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Poster

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Program #/Poster #: PSTR364.09/U8

Topic: H.04. Executive Functions

Title: Prefrontal cortex dopamine responds to the total valence of stimuli

Authors: *Y. YANG, M. DESIMONE, W. PARENT, I. T. ELLWOOD;
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Abstract: Dopamine in the prefrontal cortex (PFC) is important for normal cognition, working memory and cognitive flexibility, while its dysfunction has been proposed to underly some symptoms of psychiatric diseases, such as schizophrenia. PFC dopamine has been shown to be released primarily following aversion, with much less release following rewards, which is surprising given its role as modulator of cognitive processes that are related to both positive and negative valence. Here, we present two findings that clarify PFC dopamine's response to rewarding and aversive stimuli. First, we record dopamine release in the prelimbic cortex (PL) during social interactions between mice and find that pairings that are more rewarding are associated with increased PFC dopamine release. Notably, when female mice meet male mice in estrus, when they are receptive to mating, there is more dopamine release than when they are in diestrus. Second, we examine dopamine release in cases of mixed valence, in which mice are presented stimuli that are both rewarding and aversive at the same time. We find that PFC dopamine concentrations cannot be interpreted as function of the net valence (reward – aversion) of the stimuli and propose that PFC dopamine release is better explained as function of total valence (reward + aversion). Finally, we discuss whether PFC dopamine can be considered as a novelty or salience signal and how its responses may fit with its role in cognitive processes.

Disclosures: Y. Yang: None. **M. Desimone:** None. **W. Parent:** None. **I.T. Ellwood:** None.

Poster

PSTR364: Prefrontal Mechanisms in Non-Primate Mammals

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR364.10/U9

Topic: H.04. Executive Functions

Support: NINDS Intramural Research Program (ZIA NS003168)
NIMH Intramural Research Program (ZIA MH002970)

Title: Optical reshaping of hippocampal input-prefrontal interneuron interactions to influence mouse spatial cognition

Authors: S. E. SILVERSTEIN[1], M. S. DESHPANDE[1], E. VAUGHAN[1], T. T. CLARITY[1], C. M. ALOIMONOS[1], M. HSIANG[1,2], H. E. YARUR[3], V. TSAI[3], H. A. TEJEDA[3], J. A. GORDON[1,4], ***D. A. KUPFERSCHMIDT**[1];
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Abstract: Functional connectivity between rodent ventral hippocampus (vHPC) and medial prefrontal cortex (mPFC) supports spatial working memory (SWM). Inhibition of vHPC inputs to mPFC or distinct subclasses of mPFC interneurons (INs) induces vHPC-mPFC dysconnectivity and SWM deficits. Further, activity-induced plastic changes in vHPC-mPFC circuits have been shown to modify performance in SWM-related tasks. Together, these findings suggest that vHPC inputs onto mPFC INs, and their plasticity, are uniquely positioned to influence SWM. By combining in vivo optogenetic stimulation of vHPC inputs to mPFC with optical recordings of mPFC IN activity, we characterized activity-induced plasticity of functional connections between vHPC inputs and various mPFC IN populations, and tested how reshaping these connections alters SWM task-related IN activity and performance in male and female wildtype mice. Repeated stimulation of vHPC inputs persistently strengthened and weakened their functional connectivity with somatostatin (SST)- and vasoactive intestinal polypeptide (VIP)-expressing INs, respectively. These changes were accompanied by enhanced and suppressed non-evoked, endogenous activity dynamics in SST- and VIP-INs. Using whole-cell slice electrophysiology, we found that optically evoked monosynaptic excitatory transmission from vHPC terminals was reduced by prior in vivo stimulation in VIP-, but not SST-INs, implicating vHPC input synapses on mPFC VIP-INs as a primary locus of the in vivo plasticity. In the T-maze delayed non-match-to-sample SWM task, SST-IN activity increased during the sample and choice phases and diminished across the delay phase; VIP-INs showed generally opposing activity patterns. These patterns were also dynamic across SWM task acquisition. Although prior vHPC input stimulation did not alter these overall SST- or VIP-IN activity patterns, it paradoxically increased VIP-IN activity in early training, particularly in the delay and choice phases of the task. Higher initial VIP-IN activity in these phases associated with lower accuracy across SWM task acquisition. Accordingly, in mice that successfully learned the SWM task, prior vHPC input stimulation appeared to slow task acquisition. Together, these findings reveal cell-type-specific plasticity within intact vHPC-mPFC circuits that reshapes the mPFC microcircuit activity dynamics supporting spatial cognition.

Disclosures: S.E. Silverstein: None. **M.S. Deshpande:** None. **E. Vaughan:** None. **T.T. Clarity:** None. **C.M. Aloimonos:** None. **M. Hsiang:** None. **H.E. Yarur:** None. **V. Tsai:** None. **H.A. Tejeda:** None. **J.A. Gordon:** None. **D.A. Kupferschmidt:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.01/Web Only

Topic: H.07. Long-Term Memory

Support: Departamento de Ciencias de la Salud UAM Lerma

Title: Functional role of Arc in the consolidation of social memory within the amygdala

Authors: V. DIAZ, *K. GUZMAN-RAMOS;
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Abstract: Social memory allows individuals to adapt to the environment and learn from others (social learning), recognize relatives or conspecifics (social recognition), and the formation and stability of social groups, mate selection, among others. One of the brain regions involved in this type of memory is the amygdala since its inactivation induces a deficit in the formation of a social recognition task, and protein synthesis within this structure underlies the social memory trace consolidation. However, the proteins that participate and regulate this process are yet to be determined. Arc (activity regulated cytoskeleton-associated protein) is an immediate early gene expressed in response to synaptic input but is also a critical modulator of neuronal plasticity that might play a preponderant role in social memory consolidation within the basolateral amygdala. To assess this, we used the social recognition task, where an adult male mouse interacts with a juvenile conspecific, 24 h later, the same familiar mouse and a novel mouse are exposed. The behavioral response of the test mouse is recorded and the interaction time with each one is determined. On the familiarization phase, the test mice were injected with antisense oligonucleotides in the amygdala to inhibit Arc synthesis; the control group received a scrambled oligonucleotide and underwent, the same task and behavioral evaluation. Our results indicate that the antisense oligonucleotide administration decreased Arc protein within the basolateral amygdala and impaired the recognition of the familiar mouse, since the test mouse spent the same amount of time exploring both familiar and “novel” mice compared to the group that received scrambled oligonucleotide, which spent more time exploring the novel mice. These results show the functional relevance of Arc in the formation of social memory in the basolateral amygdala, since they indicate that the expression and synthesis of the Arc protein, triggered by the input of social information, is necessary for the trace consolidation of this type of memory.

Disclosures: V. Diaz: None. **K. Guzman-Ramos:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.02/U10

Topic: H.07. Long-Term Memory

Support: NIH R00 AG068306
NIH T32-NS007421

Title: Unraveling the transcriptomic profile associated with memory consolidation in the retrosplenial cortex

Authors: *S. BLIESE, B. BASU, S. BEYER, S. CHATTERJEE;
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Abstract: Memory consolidation, or the process of converting newly acquired information into stable long-term memories, involves precisely timed transcriptional and translational events after learning. Neuronal ensembles that exhibit these events in response to learning are known as engram cells, and their activity plays a vital role in the accurate recall of a memory. The retrosplenial cortex (RSC) is a brain region that displays engram ensembles, and their activity is critical for long-term memory. Therefore, it is important to investigate the cell type-specific transcriptional changes that occur during memory consolidation within the RSC. To address this, we utilized state-of-the-art spatial transcriptomic approaches and cell-type-specific translational affinity purification (TRAP) techniques to uncover the molecular signature within the RSC during the consolidation of spatial memory. Male mice 3-4 months of age were trained in the spatial object recognition (SOR) task, and the spatial gene expression within the RSC was mapped one hour after learning, a critical window for memory consolidation. This was further compared to home-cage control animals, and pseudo-bulk analysis of the spatial transcriptomics data showed an upregulation of genes typically associated with memory consolidation, such as *Fos*, *Egr1*, *Arc*, and *Nr4a1*, following learning in the RSC. Next, we investigated neuronal subtypes within the RSC that were critical to spatial memory consolidation. Using a chemogenetic approach, we precisely inhibited the activity of excitatory neurons immediately after learning within the RSC. This modulation of RSC excitatory neurons during early time windows of memory consolidation resulted in long-term spatial memory impairments in the SOR task. To further investigate the molecular signature of the excitatory neurons after learning, we performed translational profiling (TRAP-seq) of mRNA within the RSC after learning. The differentially expressed genes from the ribosomal-bound RNA were highly correlated to the spatial transcriptomics data from the RSC after learning. Taken together, our results uncover a unique molecular signature of memory consolidation within the RSC and demonstrate the role of the RSC excitatory neurons during the critical early time points of memory consolidation.

Disclosures: S. Bliese: None. **B. Basu:** None. **S. Beyer:** None. **S. Chatterjee:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.03/U11

Topic: H.07. Long-Term Memory

Support: 5R01AG066189

Title: Investigating the form and function of CPEB2 aggregates in mammalian long-term memory

Authors: *O. P. KIM, C. TOMOMORI-SATO, S. SATO, K. SI;
The Stowers Inst. for Med. Res., Kansas City, MO

Abstract: Memory formation requires experience-dependent changes in synapse function involving a local increase in protein synthesis and global increase in gene expression. Consequently, the lifetime of a memory depends on the ability for these synaptic changes to persist and withstand events such as protein degradation or molecular turnover. Therefore, a central question in the field of long-term memory is how and what maintains an altered synaptic state for extended periods of time. Cytoplasmic polyadenylation element binding proteins (CPEBs) are a family of RNA-binding proteins that regulate translation. A subset of these proteins repress translation in their monomeric state. Upon neural activity, however, the same CPEBs form amyloids to activate translation. Contrary to the deleterious view of amyloids in the brain, CPEB amyloids are necessary to maintain long-term changes in synaptic function and long-term memory in invertebrates. Vertebrates encode four CPEB proteins (CPEB1-4) of which CPEB2 is the most elusive. As the proposed ortholog to invertebrate CPEBs, CPEB2 encodes a long isoform (CPEB2-L) with a highly disordered prion-like domain capable of forming protein assemblies in the brain. We propose that long-lasting changes in synaptic function are in part due to self-sustaining CPEB amyloids, thus sustaining long-term memories for weeks, months, and even decades.

Disclosures: O.P. Kim: None. **C. Tomomori-Sato:** None. **S. Sato:** None. **K. Si:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.04/U12

Topic: H.07. Long-Term Memory

Support: NIH F31 (1 F31 AG084268 -01)

Title: Phosphorylation status of HDAC3 modulates long-term memory formation and synaptic plasticity in young adult and aging mice

Authors: *A. C. RODRIGUEZ[1], E. A. KRAMÁR[2], D. P. MATHEOS[2], J. S. ROUNDS[3], A. A. KEISER[1], A. S. AUGUSTYNSKI[1], T. N. DONG[4], M. A. WOOD[5];
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Abstract: Long-term memory formation is negatively regulated by histone deacetylase 3 (HDAC3), a transcriptional repressor. Emerging evidence suggests that post-translational phosphorylation of HDAC3 at its unique S424 residue is critical for its deacetylase activity in transcription. To date, HDAC3 S424 phosphorylation appears to be important for HDAC3 deacetylase activity in cancer cells, metabolism, and in Parkinson's disease. However, it's unknown if HDAC3 S424 phosphorylation is an additional mechanism that is necessary for HDAC3's ability to modulate long-term memory formation. We hypothesized that HDAC3 S424

phosphorylation is a mechanism that regulates HDAC3 activity, and thereby, regulates long-term memory formation in the hippocampus. Furthermore, we hypothesized that hyper-phosphorylation of HDAC3 S424 in the aging brain contributes to age-related memory impairments. To test this, we developed viruses to express HDAC3 phospho-mimetic mutations for either constitutively active deacetylase activity (phospho-mimic) or constitutively inactive deacetylase activity (phospho-null). We assessed the consequences of HDAC3 phospho-mimic and phospho-null expression in the dorsal hippocampus on long-term memory formation and synaptic plasticity in young adult male cohorts of mice (3 mo). We also assessed whether HDAC3 phospho-null expression could ameliorate deficits in long-term memory formation and synaptic plasticity in aging male and female cohorts of mice (18 mo). We tested long-term memory formation in mice with an object location memory (OLM) task and then measured synaptic plasticity with slice electrophysiology in CA1. We found that young adult male mice expressing the phospho-mimic virus in dorsal hippocampus exhibited *impaired* OLM performance and synaptic plasticity in CA1, compared to mice expressing the empty vector virus. However, young adult male mice expressing the phospho-null virus exhibited *enhanced* OLM performance and synaptic plasticity compared to controls. We also found that expression of the phospho-null virus in aging male and aging female mice ameliorated long-term memory and synaptic deficits compared to age-matched controls. Overall, our findings indicate that HDAC3 S424 phosphorylation is critical for hippocampal-dependent forms of memory and synaptic plasticity and that HDAC3 S424 phosphorylation can bidirectionally regulate long-term memory formation and synaptic plasticity.

Disclosures: A.C. Rodriguez: None. **E.A. Kramár:** None. **D.P. Matheos:** None. **J.S. Rounds:** None. **A.A. Keiser:** None. **A.S. Augustynski:** None. **T.N. Dong:** None. **M.A. Wood:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.05/U13

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

Support: NIH Grant DA047981
NIH Grant DA00726

Title: Viral interference of HDAC3 in the infralimbic to nucleus accumbens pathway promotes appetitive Pavlovian extinction

Authors: C. CORBETT[1], R. C. DERMAN[2], D. P. MATHEOS[3], M. A. WOOD[4], ***M. LATTAL**[5];
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Abstract: The ability to modify unwanted behaviors is a central goal of therapeutic approaches to many psychological disorders. This approach relies on classical extinction methods to eliminate unwanted behaviors. The loss of behavioral expression during extinction is achieved by breaking the associative contingency between a conditional stimulus (CS) and its outcome. This loss of behavior is often short lived with retention of the original associative memories being revealed through a range of testing conditions, such as contextual renewal, reinstatement, spontaneous recovery. A less common but powerful approach to unmasking the intact memories following extinction is the use of Pavlovian-to-instrumental transfer (PIT). In this approach, animals receive Pavlovian conditioning and instrumental training, followed by Pavlovian extinction, and then finally a PIT test. It has been shown that even following extensive extinction, animals will manifest PIT (augmentation of instrumental actions that produce the same outcome as signaled by a CS) that is comparable to animals who never underwent extinction. The mechanism by which memories are preserved across extinction remains unclear. One viable molecular mechanism for this is the enzyme histone-deacetylase-3 (HDAC3). In the nucleus, HDAC3 plays an important role in the suppression of gene expression by deacetylating histones and increasing its binding to DNA thereby blocking access to transcriptional machinery needed for gene expression. In the current experiment, we examine whether viral interference with HDAC3 in the infralimbic cortex and its efferent connection with the NAc contributes to the preservation of memories across Pavlovian extinction. Forty male Long-Evans rats received instrumental training, in which lever pressing led to food pellets. Next, they received Pavlovian conditioning and learned to discriminate between a CS+ that was paired with pellets and a control CS- that was nonreinforced. Rats then received injection of a retrograde-Cre virus into the NAc and a Cre-dependent HDAC3-point mutant vector into the IL (or a DIO-mCherry control). This was followed by Pavlovian extinction and a PIT test, during which rats were given access to the levers, and the CSs from conditioning were presented intermittently. We found that rats given HDAC3-PM injections showed modestly accelerated extinction of Pavlovian conditioning and exhibited weaker PIT than animals given mCherry injection. The data suggest that IL-HDAC3 plays a role in conserving memories across Pavlovian extinction.

Disclosures: C. Corbett: None. **R.C. Derman:** None. **D.P. Matheos:** None. **M.A. Wood:** None. **M. Lattal:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.06/U14

Topic: H.07. Long-Term Memory

Support: NIH R01 MH087463

Title: Lysine Crotonylation is a Novel Epigenetic Modulator of Hippocampal Memory Consolidation

Authors: *U. MUKHERJEE[1,2,3,4], Y. VANROBAEYS[1,5,3,4], B. BASU[1,3,4], T. ABEL[1,3,4], S. CHATTERJEE[1,3,4];
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Abstract: Histone post-translational modifications (PTMs) are critical in regulating the transcriptomic events that facilitate memory consolidation. Histone lysine acetylation (Kac) has been the most extensively studied short-chain lysine acylation in the context of long-term memory storage. Emerging evidence indicates that most of the 'writers' (lysine acetyltransferases, KATs) and 'erasers' (lysine deacetylases, KDACs) of histone Kac regulate several other non-acetyl histone acylation marks. Lysine crotonylation (Kcr) is one such non-acetyl histone acylation that is modulated by enzymes regulating histone Kac. Transcriptional regulation by histone Kcr has been implicated in several biological processes, such as DNA damage repair, spermatogenesis, and neural stem cell differentiation. Intriguingly, studies in cell-free systems have revealed that histone Kcr is a more potent activator of gene expression than histone Kac. Given that long-term memory storage requires precise spatiotemporal control of gene expression, we hypothesized that histone Kcr would be integral to the epigenetic machinery that regulates memory consolidation. Here, we provide the first evidence supporting the role of lysine crotonylation underlying hippocampal memory storage. We demonstrate that spatial learning in mice increases Kcr levels in the hippocampal subregions CA1 and subiculum during the early temporal window of memory consolidation. Additionally, we show that pharmacological stimulation of histone Kcr immediately after learning enhances hippocampal long-term memory. Conversely, silencing histone Kcr levels in the hippocampus using a viral-based approach leads to impairments in long-term spatial memory. Next, we utilized single-nuclei multiomics to decipher a molecular explanation underlying the long-term memory enhancement observed in response to Kcr activation. Our multiomic analyses revealed that enhancing Kcr levels during the critical temporal window of memory consolidation results in the differential expression of genes involved in glutamate receptor activity and calcium ion binding within the principal neuronal populations of CA1 and subiculum. Altogether, these findings provide substantial evidence in support of histone Kcr as a molecular switch that bidirectionally regulates hippocampal memory storage. Our study elucidates a unique epigenetic mechanism underlying hippocampal memory consolidation and offers the conceptual framework to develop novel therapeutic strategies against cognitive impairments associated with neurological disorders.

Disclosures: U. Mukherjee: None. **Y. Vanrobaeys:** None. **B. Basu:** None. **T. Abel:** None. **S. Chatterjee:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.07/U15

Topic: H.07. Long-Term Memory

Title: Prediction Error and Memory Strength Affect the Initiation of Memory Reconsolidation

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Abstract: Extensive animal and human studies have investigated memory reconsolidation- where consolidated memories are reactivated to make them labile and susceptible to change. Prediction error (PE) has been found as one of the necessary boundary conditions for destabilizing memory. Supporting data suggests that PE or violation of an anticipated event can destabilise a memory upon retrieval. A discord in expectation can disrupt memory trace, insufficient PE can lead to inactive memory trace and excessive PE leads to extinction. Another important boundary condition is the strength of memory- strongly encoded memories are found resistant to destabilisation and require additional manipulation to render destabilisation.Our study aimed to demonstrate how memory reconsolidation is influenced by prediction error and memory strength. On a sample of sixty participants, we used CS reactivation and different levels of expectancy violation. A three-day fear conditioning paradigm was used- on Day 1: Acquisition (50% and 100%), Day 2: CS Reactivation(single and multiple), and Day 3: extinction learning and reinstatement.Subjective measures, behavioural and SCR data were recorded. In our assessment, we found that a single PE was insufficient in preventing the return of fear for stronger memories. Reinstatement of fear was prevented only in the condition of partial reinforcement rate using different retrieval strategies (multiple PE and single CS reactivation) which was not the case in continuous reinforcement. Our findings suggest that the induction of disruption using PE in consolidated memories depends on the strength of the memory. Hence, the importance of expectancy violation in destabilising consolidated memory and its dependence on the strength of memory suggests that reconsolidation can be achieved if we can explore boundary conditions-related factors. The findings of the study can be utilised in chalking out clinical interventions for emotional memory related disorders.

Disclosures: T. Paul: None. **M.K. Asthana:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.08/U16

Topic: H.07. Long-Term Memory

Support: AG028271
AG067061

Title: Consumption of refined-ingredient diets impair long-term memory independent of macronutrient composition in aged rats

Authors: *M. J. BUTLER[1], A. A. SANCHEZ[1], S. M. MUSCAT[1], B. D. ALVAREZ[2], S. MACKEY-ALFONSO[3], J. BLACKWELL[4], R. M. BARRIENTOS[3];
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Abstract: We have previously shown that consumption of a high fat diet impaired long-term memory in aged rats via exaggerated neuroinflammation, relative to young and standard chow-fed controls. However, the specific contribution of dietary fat versus other macronutrient differences in the diets to the memory impairment is unknown. Here, we examined the effects of consumption of purified diets containing differing concentrations of fats, sugar, and refined carbohydrates to begin to disentangle the contribution of each of these macronutrients to memory decline. Specific diets were: 1) grain-based standard chow control diet containing low-fat no-sugar; 2) purified low-fat low-sugar diet; 3) purified medium-fat low-sugar diet; 4) purified medium-fat high-sugar diet; 5) purified low-fat high sugar; or 6) purified high-fat low sugar diet. Following diet consumption, rats underwent either contextual fear conditioning to test both hippocampal- and amygdalar-dependent memory function, or brain tissues were collected for gene expression and proteomics analysis. Our results indicate that contextual fear memory was impaired in aged rats fed the high-fat low-sugar diet, but not in any of the other groups. Furthermore, cued-fear memory was impaired in aged rats that consumed purified diets, regardless of macronutrient composition, relative to aged rats fed the standard chow diet. This memory impairment in aged rats was associated with dysregulated interleukin-1 beta and interferon gamma gene expression in the amygdala. Our proteomics analysis revealed hundreds of dysregulated proteins in the aged amygdala by purified diet consumption, relative to chow. Importantly, while there were subtle differences in specific proteins between purified diets, biological pathway analysis indicated they all had altered proteins associated with mitochondrial dysfunction. Overall, this study suggests that purified diets, which all contain refined sources of carbohydrates and lack fiber, contribute to amygdala-dependent memory impairment in aged rats, perhaps via inflammatory and metabolic mechanisms, while high dietary fat consumption plays a unique role in the deterioration of hippocampal-dependent memory in aged rats.

Disclosures: M.J. Butler: None. **A.A. Sanchez:** None. **S.M. Muscat:** None. **B.D. Alvarez:** None. **S. Mackey-Alfonso:** None. **J. Blackwell:** None. **R.M. Barrientos:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.09/U17

Topic: H.07. Long-Term Memory

Support: MH122414
MH131587
AG081851

AG071523
AG079292

Title: Sex-specific role of degradation-independent lysine-63 polyubiquitination in fear memory reconsolidation

Authors: *S. E. KINCAID, N. PREVEZA, T. J. JAROME;
Virginia Tech., Blacksburg, VA

Abstract: Strong evidence suggests the ubiquitin-proteasome system, which controls most protein degradation in cells, is a critical regulator of fear memory consolidation and reconsolidation following retrieval. However, ubiquitination is complex and many forms of ubiquitination are unrelated to the canonical protein degradation process. The most abundant ubiquitin modification in cells is lysine-48 polyubiquitination, which is preferentially targeted by the proteasome for degradation. However, the second most abundant form, K63 polyubiquitin chains, are degradation-independent. Importantly, we have recently shown that K63 polyubiquitination selectively regulates fear memory formation, or consolidation, in the amygdala of females, but not males. Whether K63 polyubiquitination has a sex-selective role in other stages of memory storage remains unknown. Here, we utilized a K63-specific Tandem Ubiquitin Binding Entity (TUBE) and liquid chromatography mass spectrometry (LC/MS) to identify proteins targeted by K63 polyubiquitination in the amygdala of male and female rats following contextual fear memory retrieval. In males, we identified 19 proteins that gained and 5 proteins that lost K63 polyubiquitin after contextual fear memory retrieval with the highest positive fold changes found in opioid binding protein, microtubule associated protein, and matrin-3, which are associated with membrane receptors, cell structure and synaptic depression. Conversely, in females we found only 4 proteins that gained K63 polyubiquitin following retrieval. These proteins were mitochondrial and microtubule associated proteins. These data suggest that, unlike what we observed during the consolidation process, both males and females have increased K63 polyubiquitination in the amygdala following memory retrieval, though the process is more robust in males. Together these data suggests that K63 polyubiquitin chains may have sex-specific, dissociable roles during fear memory consolidation and reconsolidation.

Disclosures: S.E. Kincaid: None. **N. Preveza:** None. **T.J. Jarome:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.10/U18

Topic: H.07. Long-Term Memory

Support: NIH Grant MH122414
NIH Grant MH131587
NIH Grant AG081851

NIH Grant AG071523
NIH Grant AG079292

Title: Aberrant, sex-specific changes in protein SUMOylation aged hippocampus correlate with age-related memory loss

Authors: *M. TURNER[1,2], Y. BAE[3], M. PATRICK[3], N. PREVEZA[3], T. J. JAROME[3];
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[3]Virginia Technol., Blacksburg, VA

Abstract: Age-related memory loss occurs in 33% of the U.S. population over the age of 70 and is a risk factor for the development of dementia and Alzheimer's disease. However, the molecular mechanisms that control age-related memory decline remain unknown. Recent evidence has indicated dysregulation of the ubiquitin-proteasome system, the primary pathway controlling protein degradation in cells, in the aged brain. However, as the focus has remained on the proteasome, much remains unknown about whether ubiquitin signaling unrelated to protein degradation becomes dysregulated in the aged brain. The small ubiquitin-like modifier (SUMO) controls protein SUMOylation in cells, a process that competes with ubiquitin and promotes protein stability, cellular localization and protein-protein interactions. Recently, we and others have reported that protein SUMOylation regulates memory formation in the brains of male and female rodents. However, it remains unknown if protein SUMOylation becomes altered in the aged brain and contributes to age-related memory loss. Here, we found sex- and age-specific changes in protein SUMOylation2/3, but not SUMOylation1, in the hippocampus. Aged (24 months) rats had impairments in hippocampus-dependent contextual fear memory relative to young (3 months) and middle-aged (12 months) rats. In female rats there was a sharp decline in SUMOylation2/3 levels in the aged hippocampus relative to young and middle-aged rats. Surprisingly, in males there was a significant increase in SUMOylation2/3 levels in the middle-aged and aged hippocampus, suggesting that SUMOylation levels become elevated prior to hippocampus-dependent memory impairments are observed. Together, these data suggest that sex-specific, aberrant changes in hippocampal protein SUMOylation may be contributing to age-related memory loss. Current experiments are testing if CRISPR-dCas9-mediated manipulation of SUMOylation in the aged hippocampus can restore memory loss across the lifespan in a sex-specific manner.

Disclosures: M. Turner: None. **Y. Bae:** None. **M. Patrick:** None. **N. Preveza:** None. **T.J. Jarome:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.11/U19

Topic: H.07. Long-Term Memory

Support: MH122414
MH131587
AG081851
AG071523
AG079292

Title: Rpn13 as a potential sex-specific regulator of proteasome function during fear memory formation

Authors: *Y. BAE[1], S. E. KINCAID[1], P. GWIN[2], N. PREVEZA[1], M. PATRICK[2], T. J. JAROME[1];
[1]Sch. of Animal Sci., Virginia Technol., Blacksburg, VA; [2]Sch. of Neurosci., Virginia Technol., Blacksburg, VA

Abstract: Post-traumatic stress disorder (PTSD) affects approximately 5% of adults in the U.S., with females exhibiting 2-3 times higher susceptibility than males. While PTSD disproportionately affects females, little is known about the underlying central mechanisms responsible for these sex differences. Previous studies have shown protein degradation through the ubiquitin-proteasome system (UPS) is critical for fear memory formation in the amygdala in both sexes. However, little is known about how increased proteasome function is coordinated in response to learning and if this differs between males and females. Importantly, the specific role of individual proteasome subunits in mediating sex-specific changes in proteasome function in response to learning remains poorly understood. Here, we found that RPN13, a non-essential 19S subunit that can be incorporated into the proteasome structure to enhance function, had significantly increased expression in the amygdala of females, but not males, following contextual fear conditioning. This suggests that RPN13 may be incorporated into the proteasome structure to accelerate proteasome function during fear memory formation in females. To test this idea, current experiments are testing if CRISPR-dCas9-mediated repression of the RPN13 coding gene, *ADRM1*, in the amygdala leads to reductions in proteasome function and fear memory formation specifically in females. Together, these findings will shed light on the role of RPN13 as a critical, sex-specific regulator of proteasome function during fear memory formation.

Disclosures: Y. Bae: None. **S.E. Kincaid:** None. **P. Gwin:** None. **N. Preveza:** None. **M. Patrick:** None. **T.J. Jarome:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.12/U20

Topic: H.07. Long-Term Memory

Support: MH122414
MH131587

AG081851
AG071523
AG079292

Title: The alternative protein degradation regulator Midnolin controls fear memory formation in a sex-specific manner

Authors: *P. GWIN, Y. BAE, S. E. KINCAID, N. PREVEZA, T. J. JAROME;
Virginia Technol., Blacksburg, VA

Abstract: Approximately 6% of the US population suffers from post-traumatic stress disorder (PTSD), with females being 2-3 times more likely to be diagnosed than males despite experiencing fewer traumatic events. However, it remains unknown what the neurobiological mechanisms are that controls this sex difference in PTSD prevalence. Over the last decade strong evidence has emerged that ubiquitin-proteasome mediated protein degradation is a critical regulator of fear memory formation in the brain. Consistent with this, we have previously found that ubiquitin-proteasome-mediated protein degradation regulates fear memory formation in the amygdala of both male and female rats. However, surprisingly, none of our ubiquitin-specific proteomic analyses have identified immediate early gene (IEG) protein products as targets of degradation-specific ubiquitin signaling following fear learning in either sex, despite the well described increases in IEGs, such as *c-fos*, *Egr1*, *Arc* and *Npas4*, in the amygdala and other brain regions following fear conditioning. This suggests that a mechanism other than ubiquitin is involved in regulating degradation of these IEG protein products during fear memory formation. Recently, a seminal paper found that the nuclear localized protein, Midnolin, could shuttle non-ubiquitinated IEG protein products to the proteasome for degradation in cells in vitro, though this has never been studied in the brain during memory formation. Here, we found that fear conditioning increases Midnolin protein expression in the amygdala of male, but not female, rats 2 and 3 hours after behavioral training, which corresponds to previously reported increases in IEG expression. Surprisingly, siRNA-mediated knockdown of *MidN* in the amygdala enhanced fear memory in male rats but impaired it in females. These data suggest that Midnolin sex-specifically regulates fear memory formation in the amygdala. Current experiments are underway investigating Midnolin's role as an alternative, sex-specific protein degradation pathway critical for IEG clearance and fear memory formation.

Disclosures: P. Gwin: None. **Y. Bae:** None. **S.E. Kincaid:** None. **N. Preveza:** None. **T.J. Jarome:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.13/U21

Topic: H.07. Long-Term Memory

Support: MH122414
MH131587
AG081851
AG071523
AG079292

Title: Degradation-independent lysine-63 polyubiquitination negatively regulates memory formation and promotes age-related memory decline in the hippocampus

Authors: *N. J. PREVEZA[1], Y. BAE[1], M. PATRICK[1], T. J. JAROME[1], P. GWIN[2];
[1]Virginia Tech., Blacksburg, VA; [2]Virginia Tech. Neurosci. PhD Program, Blacksburg, VA

Abstract: Age-related memory loss occurs in 33% of the U.S. population over the age of 70 and is a risk factor for the development of dementia and Alzheimer's disease. However, the molecular mechanisms that control age-related memory decline remain unknown. Over 90% of protein degradation in eukaryotic cells occurs through the ubiquitin-proteasome system (UPS). In this system, the ubiquitin protein can bind to a substrate on its own or it can form a chain with multiple ubiquitin molecules in a process called polyubiquitination. There are 8 different sites at which polyubiquitination can occur on ubiquitin and the second most abundant form, lysine-63 (K63), is independent of the degradation process. Recently, we found that K63 polyubiquitination selectively regulates contextual fear memory formation in the amygdala of females, but not male, rats. It is unknown, however, if the sex-specific requirement of K63 polyubiquitination occurs in other regions of the brain that are required for contextual fear memory formation, such as the hippocampus, which is also sensitive to the aging process. Here, we found that CRISPR-dCas13-mediated knockdown of K63 polyubiquitination in the hippocampus significantly enhanced contextual fear memory in both male and female rats, a result in striking contrast to what we observed in the amygdala. These data suggest that K63 polyubiquitination is a negative regulator of memory formation in the hippocampus. Surprisingly, we found a significant increase in K63 polyubiquitination in the hippocampus of aged (24 month old) rats relative to young (3 month old) or middle-aged (12 month old) rats. These results suggest that aberrant increases in K63 polyubiquitination in the aged hippocampus may contribute to age-related memory loss. Current experiments are using proteomic approaches to identify the target proteins of K63 polyubiquitination in the hippocampus following learning, as well as CRISPR-dCas13 manipulations to test if knockdown of K63 polyubiquitination in the aged hippocampus can restore memory in advanced age.

Disclosures: N.J. Preveza: None. **Y. Bae:** None. **M. Patrick:** None. **T.J. Jarome:** None. **P. Gwin:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.14/U22

Topic: H.07. Long-Term Memory

Title: Short-term memory recall reverses scopolamine-induced memory consolidation impairment of conditioned odor aversion.

Authors: L. MONTIEL-TREJO, S. FLORES-GARCÍA, *G. ROLDAN;
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Abstract: Conditioned odor aversion (COA) is a type of classical conditioning that results from pairing an olfactory cue (conditioned stimulus, CS) with a gastrointestinal malaise (unconditioned stimulus, US). In rats, it has been observed that under suboptimal training conditions such as a long (greater than 15 min) inter-stimulus interval (ISI) or the application of low doses of the US (LiCl), long-term memory (LTM) cannot be consolidated, although the presence of short-term memory (STM) is evident. Furthermore, we have reported that under these conditions, where consolidation is not expected, it is feasible to promote this process by STM recall, a phenomenon that can be termed memory reactivation. On the other hand, it is well established that the cholinergic system plays a key role in COA, so that antimuscarinic drugs may produce a profound memory impairment. Thus, here we investigated whether a reminder induced by a single STM recall may overcome the amnesic effect of scopolamine, a non-selective muscarinic receptor antagonist. Adult male and female Wistar rats between 250-300 g were submitted to a COA protocol for 5 consecutive days as follows: on days 1 and 2, they were habituated to drink tap water for 10 min in an experimental box equipped with 4 burettes of 10 ml placed in each corner. On day 3, rats were offered water again in the presence of an almond odor source close to the drinking spout; five min later they were i.p. injected with LiCl (125 mg/kg). Scopolamine (0, 1 or 3 mg/kg, i.p.) was administered 30 min before drinking. A free-choice retrieval test was performed 4 or 48 h after conditioning to assess STM or LTM, respectively. To evaluate the effect of memory reactivation, retrieval testing was carried out twice, 4 and 48 h after training. Water consumption was quantified and the odor preference index (PI) was calculated. We found a dose-dependent amnesic effect of scopolamine on long-term odor aversion memory while STM remained unaffected. Moreover, STM retrieval reversed the effect of scopolamine, as rats retained odor aversion in the long term as well. We propose that STM recall reactivates certain muscarinic-dependent consolidation processes that were obliterated by scopolamine, overcoming its amnesic effect.

Disclosures: L. Montiel-Trejo: None. **S. Flores-García:** None. **G. Roldan:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.15/Web Only

Topic: H.07. Long-Term Memory

Support: CONAHCYT 785509

Title: Neuroprotective effect of cherry (Prunus avium) juice on memory and learning in male P90 rats after maternal lipopolysaccharide infection.

Authors: *J. J. VIRGEN-GEN[1], M. ALVARADO[2], R. I. GUZMÁN-GERÓNIMO[3];
[1]Inst. de Neuroetología, Univ. Veracruzana, Xalapa, Mexico; [2]Inst. de Neuroetología, Univ. Veracruzana, Xalapa, Veracruz, Mexico; [3]Inst. de Ciencias Básicas, Univ. Veracruzana, Xalapa, Mexico

Abstract: During maternal lipopolysaccharide (MI-LPS) infection, the neurodevelopment of the offspring is affected due to alterations in the central nervous system (CNS) by early activation of the immune system by different proinflammatory mechanisms. There are several biological compounds present in foods that provide an antioxidant, anti-inflammatory and neuroprotective effect, such as anthocyanins. Among these anthocyanin-rich foods are red fruits, cherry being one of the most consumed fruits. In this study, we evaluated the neuroprotective effect of a microwave-processed cherry extract (CE) against IM-LPS during the gestational (G) and gestational-lactation (GL) periods in male Wistar rats at postnatal age (P) 90. For this purpose, five groups (n=6 per group) were used. The control group was administered with saline (0.9% NaCl) intraperitoneally (IP) on embryonic days (E) 10,12,14; while the LPS-G, LPS-G+EC, LPS-GL and LPS-GL+EC groups received via IP a dose of LPS (50µg/kg) on days E10,12,14; in addition, the LPS-GL and LPS-GL+EC groups received via subcutaneous (SC) an injection of LPS (50µg/kg) on day P7. Once the P90 age was reached, the novel object recognition test (NOR) was performed, evaluating the parameters of total interaction with the objects, as well as the total permanence with the objects. Subsequently, a histological analysis of the hippocampus was performed in the CA1, CA2, CA3 and dentate gyrus (DG) regions to determine its cell density. During the RON test, we observed that the LPS-G and LPS-GL groups showed greater fixation for the familiar object compared to the control group during the short-term memory (STM) and long-term memory (LTM) phases; however, the groups administered with the CE showed a similar behavior to the control group, interacting longer with the novel objects. On the other hand, when determining the cell density of the experimental groups, we observed that the LPS-G and LPS-GL groups showed lower cell density in the CA1 and DG regions, contrary to the control group and the groups administered with the CE that did not show significant differences with the control group. In conclusion, the administration of CE during the G and GL periods provided a neuroprotective effect against IM-LPS, due to its biological properties, inhibiting the inflammatory mechanisms that occur during an infectious process. According to our findings, an MI-LPS during the G and GL periods generated severe damage in the ontogeny of the offspring, however, the CE provided an antioxidant and anti-inflammatory effect, inhibiting the inflammatory processes during an infection, demonstrating the great potential of the cherry as a neuroprotective food.

Disclosures: J.J. Virgen-Gen: None. **M. Alvarado:** None. **R.I. Guzmán-Gerónimo:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR365.16/U23

Topic: H.07. Long-Term Memory

Support: NIH Grant MH122414
NIH Grant MH131587
NIH Grant AG081851
NIH Grant AG071523
NIH Grant AG079292

Title: Decreases in atypical, degradation-independent linear polyubiquitin in the hippocampus correlates with aged-related memory loss

Authors: *M. PATRICK, N. PREVEZA, T. J. JAROME;
Virginia Polytechnic Inst. and State Univ., Blacksburg, VA

Abstract: Age-related memory loss affects approximately 40% of the world's population after the age of 65 and is a risk factor for the development of dementia and Alzheimer's Disease (AD). Nevertheless, there is still limited knowledge about the brain molecular mechanisms supporting the decline of memories across the lifespan. Numerous studies have reported that later in lie there are decreases in the function of the ubiquitin-proteasome system, the main regulator of protein degradation in cells. However, ubiquitin can mark proteins for fates other than destruction by the proteasome. Despite this, it is unknown how the aging process alters proteasome-independent forms of ubiquitination and how this could contribute to age-related memory loss. Here, we found that linear polyubiquitination, an atypical (non-lysine) proteasome-independent form of polyubiquitination that we previously reported is critical for memory formation in young adulthood, is significantly decreased in the aged, but not middle-aged, hippocampus, a brain region critical for memory formation and storage and known to be impacted by the aging process. Further, these reductions in linear polyubiquitination late in life correlate with deficits in hippocampus-dependent contextual fear memory. Together, these data suggest that decreases in hippocampal linear polyubiquitination could be contributing to age-related memory loss. Currently experiments are underway using unbiased proteomics and CRISPR-dCas9 mediated manipulation of linear polyubiquitination to test whether reductions in hippocampal linear polyubiquitination late in life contribute to age-related memory decline.

Disclosures: M. Patrick: None. **N. Preveza:** None. **T.J. Jarome:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR365.17/U24

Topic: H.07. Long-Term Memory

Support: NIH Grant T32MH019524
NIH Grant T32NS086750
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Title: Astrocytes secrete factors that regulate neuronal protein synthesis

Authors: *W. J. LIU[1,2], C. C. SCHULTZ[3], E. KLANN[3];
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Abstract: Neuronal protein synthesis is indispensable for long-lasting synaptic plasticity and long-term memory. Although translational regulation in plasticity and its dysregulation in disease has been well characterized in neurons, it is unknown whether this process is cell autonomous, or whether other cell types are involved. Because astrocytes are known to secrete a wide range of trophic, supporting factors that promote neuronal survival and function, we first sought to determine whether astrocytes can regulate neuronal translation. Using primary mouse astrocyte cultures, we collected astrocyte-conditioned medium (ACM) and used this ACM to treat mouse cortical neuron cultures. We labeled newly synthesized proteins using puromycin, an aminonucleoside that enters the ribosomal A site to transfer to a growing peptide. Neurons treated with ACM displayed increased puromycin signal, suggesting that astrocytes release factors that increase neuronal translation. In addition, the increase caused by ACM was further upregulated by treating astrocytes with brain-derived neurotrophic factor (BDNF) prior to ACM collection. However, BDNF-treated astrocytes did not display increased puromycin signal, suggesting that the neuronal translation enhanced by ACM is dependent on upregulation of specific astrocyte-secreted factors, rather than an increase in global astrocyte translation. To confirm that this *in vitro* observation is also present *in vivo*, we injected GFAP-hM3D-Gq or hM4D-Gi DREADDs into mouse dorsal hippocampus, then labeled newly synthesized proteins using L-azidohomoalanine (AHA), a methionine analog that is recognized by the endogeous methionyl-tRNA transferase. Consistent with our previous results, Gq and Gi-DREADD activation in astrocytes alters baseline neuronal translation *in vivo*. Although the identity of astrocyte-secreted factors that modulate neuronal translation remain to be determined, notably, removal of apolipoprotein E (APOE) from ACM leads to an increase in neuronal translation, suggesting that although the full profile of astrocyte-secreted factors exert a net positive effect, APOE exerts a negative regulatory effect. Taken together, these findings suggest that astrocytes can regulate neuronal translation in a physiological, non-cell autonomous manner that may be important for long-lasting synaptic plasticity and memory. Moreover, disruption of this astrocyte-neuron communication might underlie impaired translation observed in neurodegenerative diseases such as Alzheimer's disease. This work was supported by NIH grants T32MH019524 and T32NS086750 (W.J.L.), and NS034007 and NS122316 (E.K.).

Disclosures: W.J. Liu: None. **C.C. Schultz:** None. **E. Klann:** None.

Poster

PSTR365: Consolidation and Reconsolidation: Molecular Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR365.18/U25

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

Support: NIH R01 AG054551 to SNG
NIH R01 AG077611 to SNG

Title: The CA1 M1 muscarinic acetylcholine receptor is necessary for hippocampal memory encoding and consolidation processes

Authors: *H. LI[1], H. ZHOU[2], S. N. GOMPERTS[1];
[1]Massachusetts Gen. Hosp., Boston, MA; [2]Xuzhou Med. Univ., Xuzhou, China

Abstract: Cholinergic activity is critical for hippocampal function, and muscarinic receptor antagonists cause memory impairment. Among all acetylcholine receptors (AChRs) subtypes, the M1 mAChR is strongly expressed in the hippocampus and cortex and has multiple effects that may contribute to its role in memory and cognition. It depolarizes cells, drives IP3-mediated release of calcium from intracellular stores, regulates NMDA-receptor signaling, and contributes to synaptic plasticity. However, the role of the M1 mAChR in CA1-dependent systems level memory processes is not yet well understood. Here we investigated the effects of hippocampal CA1 mAChR deletion on hippocampal functions linked to memory encoding and consolidation processes. The CA1 M1 mAChR was deleted from a “floxed” M1 mAChR mouse line using stereotaxic injection of AAV-hsyn-Cre-mCherry. Injection with AAV-hsyn-mCherry was used as a control. We acquired electrophysiological recordings together with simultaneous dynamic calcium imaging with GCaMP6f in hippocampal CA1 of CA1-m1KO mice (n=7) and control mice (n=9) across the sleep-wake cycle. CA1-m1KO mice showed impaired memory performance in the novel object location task. In CA1-m1KO mice, place cells acquired during exploratory behavior on a linear track showed reduced spatial information and larger place field. Hippocampal theta-gamma phase amplitude coupling was reduced both in exploratory behavior and offline, in REM sleep. In slow wave sleep, CA1-m1KO mice showed diminished coordination of cortical slow oscillations and hippocampal sharp wave ripples. Together, these results show that the CA1 M1 mAChR contributes to both online memory encoding and offline memory consolidation processes.

Disclosures: H. Li: None. **H. Zhou:** None. **S.N. Gomperts:** None.

Poster

PSTR366: Aging and Mechanisms of Hippocampal Function

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.01/U26

Topic: H.08. Learning and Memory

Support: S10 OD025016
T32AG082631-01
McKnight Brain Research Foundation

Title: Using Bias-free Classification of Multi-parametric MRI to Identify Age-related Changes in the Ex-Vivo Female Bonnet Macaque Brain

Authors: *L. DIECKHAUS[1], K. MCDERMOTT[1], D. T. GRAY[2], C. A. BARNES[3], E. B. HUTCHINSON[4];
[1]Univ. of Arizona, Tucson, AZ; [2]Physiol., UCLA, Los Angeles, CA; [3]Evelyn F. McKnight Brain Inst., Univ. of Arizona, Tucson, AZ; [4]Biomed. Engin., Univ. of Arizona, Tucson, AZ

Abstract: There are several Magnetic resonance imaging (MRI) quantitative maps that may be sensitive to age-related brain changes, but it is unclear which maps offer the most information. In addition to discerning which singular MRI quantitative map provides the most sensitivity to age-related changes, it is possible that a combination of maps may be more informative. We used a voxel-wise binary classifier to identify aged-related changes across the female bonnet macaque whole brain with multi-parametric MRI datasets, which were composed of different MRI maps. Non-human primates provide an excellent model to determine lifespan-related brain changes with MRI. Additionally, *ex-vivo* whole brain imaging allows for collection of a variety of MRI map types at high resolution that would otherwise be time constrained in-vivo. Diffusion and relaxometry derived MRI maps were obtained at 200-to-600-micron resolution isotropic in seven female bonnet macaque *ex-vivo* brain specimens ranging in age from 10-34 years. Diffusion-based maps included Fractional Anisotropy, Axial Diffusivity, Radial Diffusivity, and Trace, which measure diffusion of water and assesses white matter tract geometry. Relaxometry-based maps included T2, R2star, Myelin Water Fraction, and Bound Pool Fraction, which measure the biophysical properties of tissue such as myelin and iron content. These maps were warped to a template space for group analysis. We classified adult (14-21 years, n=3) vs. aged (28-34 years, n=4) brains using three MRI datasets: all metrics, diffusion-only, and relaxometry-only. For each voxel in the brain, the accuracy of predicting aged versus adult was calculated. Brain areas that showed significant differences included the thalamus, hippocampus, and amygdala. The all metrics dataset outperformed diffusion and relaxometry only models significantly in the thalamus (Cohen's D range=3.64,5.14, diffusion-only and relaxometry-only respectively; $p<0.001$) and hippocampus (Cohen's D= 3.4 ,3.76, diffusion-only and relaxometry-only respectively; $p<0.001$). In the amygdala, the all metrics dataset outperformed the relaxometry-only dataset significantly (Cohen's D=2.2, $p<.01$), but not the diffusion-only dataset ($p=.23$). There was no significant difference between diffusion-only and relaxometry-only datasets, except for in the amygdala (Cohen's D=1.4, $p<.05$). These results suggest a mixed effect of MRI map types on identifying age-related changes in the brain.

Disclosures: L. Dieckhaus: None. **K. McDermott:** None. **D.T. Gray:** None. **C.A. Barnes:** None. **E.B. Hutchinson:** None.

Poster

PSTR366: Aging and Mechanisms of Hippocampal Function

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.02/U27

Topic: H.08. Learning and Memory

Support: RO1 AG003376
McKnight Brain Research Foundation

Title: Relationships between cognition, MRI-based regional gray matter volume and amyloid and tau histopathology across the lifespan of male and female rhesus macaques.

Authors: *C. BARNES[1], M. PERMENTER[2], J. A. VOGT[3], K. CHEN[4], T. G. BEACH[5]; [1]Univ. of Arizona, Tucson, AZ; [2]UC Davis, Davis, CA; [3]NSMA/California Natl. Primate Res. Ctr., Woodland, CA; [4]Arizona State Univ., Phoenix, AZ; [5]Banner Sun Hlth. Res. Inst., Sun City, AZ

Abstract: Primary histopathological correlates of Alzheimer's disease (AD) include Aβ plaques abnormally phosphorylated tau (ptau), neuron death and synapse loss, which in its severe form is accompanied by dementia. All of these features are represented in the NIA-AA Research Framework (ATN) designed for diagnosing AD in living people using imaging and biofluid biomarkers for amyloid (A), tau (T), and neurodegeneration/neural injury (N) (Jack et al., 2018). Another common feature of the brains of AD patients involves cerebral amyloid angiopathy (CAA). There have been no experiments that examined potential relationships between cognition, regional brain distribution of amyloid plaques, CAA, ptau and MRI-determined gray matter volumes in the same group of behaviorally characterized nonhuman primates. Furthermore, ATN classification has not been conducted in nonhuman primates. Here, all of these variables were examined in a group of 32 male and female rhesus macaques ranging in age from 7 to 33 years. Amyloid plaques and/or cerebral amyloid angiopathy was found in at least one brain region in 13 of 17 monkeys over 22 years of age, and ptau was found in at least one brain region in 6 of 17 monkeys over 22 years of age; the latter was indicative of "pretangles" but no actual neurofibrillary tangles were observed in any monkey. There was a sex difference in the pattern of neuropathological findings in the brains of monkeys over 22 years, with males having more ptau than females, and females having more plaques and CAA than males. When ATN staging was conducted, those monkeys with "triple positive" ATN status had significantly slower learning and poorer retention scores in a Delayed NonMatching-to-Sample task than did monkeys who were "triple negative"; but no monkey had amyloid or ptau levels or distributions severe enough to indicate a diagnosis of AD, nor were any of the cognitive impairments severe enough to be consistent with dementia. As has been observed previously, rhesus macaques over 22 years of age had lower regional grey matter volumes than did young animals, and the most striking behavioral correlates of the lower gray matter volumes in older monkeys was found in both acquisition and retention of an Object Discrimination task. Together these data suggest that not all aging primates develop AD histopathology or dementia.

Disclosures: C. Barnes: None. **M. Permenter:** None. **J.A. Vogt:** None. **K. Chen:** None. **T.G. Beach:** None.

Poster

PSTR366: Aging and Mechanisms of Hippocampal Function

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Program #/Poster #: PSTR366.03/U28

Topic: H.08. Learning and Memory

Support: R01 AG003376
McKnight Brain Research Foundation
CNPRC Center Grant RR000169

Title: Changes in noradrenergic receptor density in hippocampus across the lifespan of the rhesus macaque

Authors: *K. MCDERMOTT[1], I. SINAKEVITCH[2], V. SHAH[1], C. A. BARNES[2];
[1]Univ. of Arizona, Tucson, AZ; [2]Evelyn F. McKnight Brain Inst., Univ. of Arizona, Tucson, AZ

Abstract: The Locus Coeruleus (LC) is a noradrenaline (NA)-producing brainstem nucleus with wide projections throughout the cortex. NA acts via 3 classes of receptors (α1, α2, β) and this signaling is critical for optimization of cognitive performance. Two of these receptor classes (α1 and β) lead to increased likelihood of cell excitability, and the third (α2a) tends to diminish cell responsiveness. Some autoradiographic studies have shown age- and disease-related decreases in α1 and α2 receptor densities. NA fiber density has not been investigated with density of all 3 NA receptor types or with respect to cognitive performance. We have previously developed a protocol for histological analysis of the NA system in rhesus macaques (McDermott et al, Program No. 574.04, Society for Neuroscience 2022). Here, we utilize coronal brainstem sections from 30 adult and aged rhesus macaques ranging in age from 7-32 years (21 to 96 human years). All monkeys underwent tests of spatial short-term memory (delayed response), object recognition memory (delayed nonmatching-to-sample), and object discrimination. We used immunofluorescence techniques to identify three NA receptors (α1, α2a, β1) and NA fibers, as well as supporting cell types known to interact with the NA system: vasculature, microglia, and astrocytes. Images from both the dentate gyrus (DG) and CA3 region of the hippocampus from each immunolabeled section were taken at 40X on a high-resolution confocal microscope. NA receptor, NA fiber, glial and vascular densities were determined using unbiased stereological techniques. These data were then assessed with respect to the age and cognitive status of the monkeys. No difference was seen in the density of NA fibers in the DG or CA3. Preliminary results reveal higher α2a and microglia density in the DG and higher density of all three NA receptor subtypes as well as astrocyte and microglia density in CA3 of aged animals. Because glial density is increased in both CA3 and DG in aging, the selective increases in density of all three NA receptor types in CA3 is not likely to be solely explained by glia but rather by increased expression in neuronal elements as well. Thus far, only retention of the object discrimination task was found to be related to NA receptor density- specifically, higher density of the excitatory β1 receptor density in CA3 in aged macaques was associated with worse retention on the object discrimination task. This suggests that optimal concentrations of the β1 NA receptor in CA3, which is critical for synaptic plasticity, may modulate interactions between

fronto-parietal, temporal and occipital cortices that are necessary for performance on the object discrimination task.

Disclosures: K. McDermott: None. **I. Sinakevitch:** None. **V. Shah:** None. **C.A. Barnes:** None.

Poster

PSTR366: Aging and Mechanisms of Hippocampal Function

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Topic: H.08. Learning and Memory

Support: R01-AG072643
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McKnight Brain Research Foundation
U19-AG073153
R01-AG045571
5R01-AG067781
P30-AG13854
P30-AG072977
R56-AG045571

Title: Identification of Alzheimer's disease- and normative age-related transcriptional changes in human middle temporal gyrus

Authors: *A. BONFITTO[1], I. S. PIRAS[1], S. SONG[1], A. ALDABERGENOVA[1], J. SLOAN[1], A. TREJO[1], J. C. TRONCOSO[2], C. GEULA[3], E. J. ROGALSKI[4], C. H. KAWAS[5], M. CORRADA[5], T. G. BEACH[6], G. E. SERRANO[7], P. F. WORLEY[8], C. A. BARNES[9], M. HUENTELMAN[1];
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Abstract: Alzheimer's disease (AD) and normal aging have demonstrable effects on the human temporal lobe. To better understand the transcriptional changes happening in the temporal lobe in the context of aging and dementia we collected a study cohort consisting of fresh frozen human brain samples from the middle temporal gyrus (n=622). In total it included 281 non-demented individuals (ND), 210 individuals with Alzheimer's disease dementia (AD), and 131 individuals with MCI or CIND (Cognitive Impairment with no Dementia) wherein each donor was

cognitively characterized while living and neuropathologically assessed following death. Each brain specimen was molecularly characterized using bulk RNA sequencing and analyzed using differential expression, gene and cell set enrichment, coexpression, key driver, and pseudotime analytical approaches. The normative aging analysis included all ND donors and identified three genes significantly down-regulated (adj-p < 0.05) in the individuals who were 65 and older: GPR26, HSPA6, and TRPC3. Additionally, we identified 472 genes that had significant differential expression in the total ND cohort. Gene Set Enrichment Analysis (GSEA) demonstrated a significant decrease in genes involved in angiogenesis with increasing age (adj-p < 2.3E-09) and Cell Set Enrichment Analysis (CSEA) showed a significant upregulation of oligodendrocyte genes and a significant downregulation of endothelial cell genes with increasing age. Finally, we observed a downregulation of inhibitory neuron genes but no changes in excitatory neuron genes in the total cohort, while genes specific to both cell types were downregulated in the ND cohort who were 65 and older. The AD-specific analysis included all ND and AD samples. We identified 4,414 genes with significant differential expression, including NPNT, GFAP, ADAMTS2, and KANK2, all of which had increased expression in the AD samples. GSEA revealed known patterns of downregulated synapse-related functions in AD while CSEA demonstrated downregulation of excitatory neuron genes and upregulation of astrocyte, endothelial cell, microglial, and pericyte genes. Coexpression identified 76 differentially-expressed modules including upregulation of the regulation of vasculature development process (top key driver gene = COL1A2) and downregulation of the regulation of postsynaptic membrane potential process (top key driver gene = EGR2). Together this cohort-based analysis empowers the comparison of AD and normative aging transcriptional effects in the middle temporal gyrus of the human brain.

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Poster

PSTR366: Aging and Mechanisms of Hippocampal Function

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.05/U30

Topic: H.08. Learning and Memory

Support: U19-AG065169 (PI: Barnes) NIH-NIA
TGen Institutional Support
Mueller Family Charitable Trust

Title: Factors associated with verbal memory performance in rural residents of the United States

Authors: *H. VENKATACHALAM[1], M. JOHNSON[1], M. DE BOTH[1], M. NAYMIK[1], M. HAY[3], R. D. BRINTON[4], C. A. BARNES[5], L. RYAN[5], M. HUENTELMAN[2];

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Abstract: Residents of rural areas are often underrepresented in research studies and clinical trials of all types. This is true for cognitive aging research and dementia-focused clinical trials. Evidence suggests that rural residents are at higher risk for dementia, demonstrate an enrichment for known risk factors, and typically receive delayed diagnoses compared to non-rural residents. We sought to investigate the factors that are associated with cognitive performance in non-demented residents of rural zip codes in the United States. We utilized our internet-based study, MindCrowd, which is over ten years old and has collected cross-sectional cognitive data from over 40,019 rural U.S. zip code residing participants. We focused here on the results from MindCrowd paired associates learning, a verbal memory task that includes three rounds of 12 word-pairs and yields a final scored result ranging from 0-36. The basic demographics of the MindCrowd rural cohort is as follows: 75% aged 50 and older, 90% White, 5% Hispanic, 19% male, and 26% high school education or less. Of note, only 12.6% of this cohort endorsed having no health/medical conditions while that same percentage is approximately doubled when the MindCrowd cohort as a whole is considered. The three most prevalent factors in rural participants are hypertension (42%), having a second-degree relative with Alzheimer's disease (31%), and depression or anxiety (26%). The three factors with the largest impact on verbal memory performance in the rural cohort were age (p=1.32e-13, beta=-0.17 word pairs per year), sex (p=7.88e-06, beta= -2.0 word pairs if male), and education (p=3.18e-05, beta=1.5 word pairs per milestone). Of note, the beta values for the three strongest predictors of verbal memory performance - age, sex, and education - were found to be similar when comparing rural and non-rural participants. Other demographic, health, medical, and lifestyle factors that had a significant influence on performance in rural residents included; number of daily prescription medications, stroke, and smoking status. In this large study of residents of rural U.S. zip codes, we demonstrate that the strongest predictors of verbal memory performance have similar impacts in rural and non-rural residents. We further characterize other factors that impact verbal memory performance within the rural cohort. While preliminary, this study represents one of the largest investigations of cognition in rural residents of the U.S. This study is a collaboration with the Precision Aging Network research team.

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Poster

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Topic: H.08. Learning and Memory

Support: U19-AG065169 (PI: Barnes) NIH-NIA
TGen Institutional Support
Mueller Family Charitable Trust

Title: A large normative aging dataset for the characterization of verbal memory performance across the lifespan.

Authors: *M. JOHNSON[1], M. DE BOTH[1], H. VENKATACHALAM[1], M. NAYMIK[1], M. HAY[2], R. D. BRINTON[3], C. A. BARNES[4], L. RYAN[4], M. HUENTELMAN[1];
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Abstract: Numerous studies have established that young adults typically perform better on episodic memory tests than older adults. However, detailed insights into how memory functions within specific age groups, and the variations in memory performance across different ages, remain limited. Additionally, there is a scarcity of research with large enough participant groups to thoroughly explore these aspects. To adequately address this, researchers need extensive datasets spanning the adult lifespan, which include diverse populations in terms of sex, educational backgrounds, race/ethnicity, and various health and lifestyle factors. Furthermore, the chosen cognitive tasks must be finely tuned to detect age-related performance shifts, avoiding any significant biases towards top or bottom scores, and should have proven sensitivity to known influential factors. Utilizing an online testing platform that we developed called MindCrowd (available at https://mindcrowd.org/), we gathered high-quality data from 143,197 adults ranging in age from 18 to 100. This data collection, which started in 2013, focused on a verbal paired associates learning task (MC-PAL). The MC-PAL task is believed to measure associative learning, a cognitive process particularly vulnerable to aging. Given its reliance on the functioning of the medial temporal lobe, various forms of this test have been used in clinical contexts to distinguish between normal age-related cognitive decline, mild cognitive impairment, and Alzheimer's disease. Using this cohort we (1) create a free portal for exploration of the data and facilitate its use to readily obtain quality norms for any given individual, considering variables that might otherwise not be available, including age, sex, education, race/ethnicity, and location (urban or rural zip code), and (2) we report on new findings from the use of MindCrowd data; including race/ethnicity specific MC-PAL predictor variables and health, medical, and lifestyle factor influences on MC-PAL performance in well-powered cohorts. MindCrowd has demonstrated the power of an internet-based approach to participant recruitment and research, particularly in the area of cognitive aging. This normative dataset represents one of the largest cognitive cohort studies to date and should serve to provide diverse comparative data for researchers interested in predicting individual differences in age-related memory performance. This study is a collaboration with the Precision Aging Network research team.

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Poster

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Topic: H.08. Learning and Memory

Support: U19-AG065169 (PI: Barnes) NIH-NIA
TGen Institutional Support
Mueller Family Charitable Trust

Title: Demographic, health, medical, and lifestyle factors associated with longitud inal verbal memory performance across the lifespan.

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Abstract: There is significant interest in identifying factors associated with changes in cognitive performance across the human lifespan. This information may help identify protective and risk factors that could be leveraged to improve age-related cognitive changes as well as ameliorate disease susceptibility. A major challenge is that most research studies tend to focus on a narrow age range which hinders an ability to extend recommendations across the human lifespan. To address this, we utilized our internet-based MindCrowd study which currently includes over 3,418 longitudinal participants that span ages from 18-97 years of age. Each of these participants include at least two longitudinal data points for verbal memory that were spaced apart by at least 365 days. The verbal memory task demonstrates upward sloping results (improvement in performance across time) for participants aged 20s-40s, relatively flattened slopes for 50s and 60s, and downward sloping results for the 70s, 80s, and 90s+. These data suggest that in the participants under 50 there are demonstrable practice effects even with at least a year interval between test sessions which then wane in the 50s and 60s and disappear entirely in those 70 and older. Using a model that included time and demographic variables to model change in performance as the outcome, we identified the following factors that were significantly predictive: age (pval 1.41e-5; beta -0.055 per year), seizures (pval 0.03; beta -2.02), and time since last test (pval 2.58e-8; beta -4.27e-6 per year). Participants that reported taking MindCrowd previously performed on average 2.1 word pairs better than those individuals who were repeat participants but did not indicate as such (pval 4.42E-12). In summary, we utilized longitudinal participants from our internet-based cognitive aging study, MindCrowd, and identified factors that were associated with longitudinal verbal memory performance across the aging spectrum under a single study design.

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Poster

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Topic: H.08. Learning and Memory

Support: AG081767
McKnight Brain Research Foundation

Title: Age-related changes in medial prefrontal cortex-ventral hippocampus theta power interactions during a spatial working memory task

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Abstract: Neural ensembles in hippocampus and mPFC play a crucial role in memory-guided navigation and decision making, a process susceptible to decline with age in mammals. These regions are connected via a unidirectional projection from the ventral hippocampus to the mPFC and damage or inhibition of this circuit leads to impairments in spatial alternation tasks (Wang et al, 2006). Rats with mPFC lesions show an impairment on spatial working memory tasks, while rats with hippocampus lesions are impaired in both spatial and working memory tasks. To test the interaction between these regions we used a spatial alternation task consisting of two interleaved components: “outbound” (working memory) and “inbound” (spatial memory). Behavioral data from young (10-13 mo) and old (24-26 mo) rats tested on this task reveals that aged rats are slower to learn both components of the task. A major deficit was observed in the aged rats’ performance on outbound trials even after reaching criteria. Because the outbound component of the task requires coordination between the hippocampus and mPFC, these interactions could be impaired in aged rats. In order to investigate the mechanisms underlying age-related impaired performance on this task, we implanted young (n=9) and old (n=3) rats with hyperdrives in both structures. Electrophysiological recordings were collected from the ventral CA1 region of the hippocampus (vHC) and in the prelimbic (PL) and infralimbic (IL) regions of the mPFC as the rats performed the spatial alternation task. Looking at electrophysiological activity prior to the rat making a choice, we observed robust theta activity (8-12Hz) in both the mPFC and vHC regions in young and old rats. Separating trials by correct and incorrect performance, we replicated the observation that theta power on correct trials was higher than on incorrect trials in the mPFC (O’Neil et al., 2013), and that this power difference was seen in both age groups. In the vHC, there was no difference in theta power between correct and incorrect trials. In young rats, there was reduced correlation of mPFC-vHC theta power prior to incorrect trials compared to correct trials. In old rats, there was no difference in mPFC-vHC theta power on the basis of performance. Overall, while there was no difference in the absolute theta power in either the vHC or mPFC regions between age groups, the theta power correlation between the regions was reduced in aged rats compared to young rats.

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Poster

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Program #/Poster #: PSTR366.09/U34

Topic: H.08. Learning and Memory

Support: AG081767
McKnight Brain Research Foundation

Title: Investigating age-related changes of mPFC neural responses to ventral hippocampus stimulation

Authors: *S. SRIVATHSA[1], A. VISHWANATH[2], S. L. COWEN[3], C. A. BARNES[4];
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Abstract: Neural ensembles in the hippocampus (HC) and medial prefrontal cortex (mPFC) play a crucial role in spatial working memory, a process susceptible to decline during aging in mammals. These regions are connected via a monosynaptic, unidirectional projection from the CA1 layer of intermediate (iHC) and ventral (vHC) hippocampus to the mPFC (Jay and Witter, 1991, J. Com. Neurol. 313:574). Damage or inhibition of this connection leads to impairments in spatial working memory tasks. Performance on spatial working memory tasks is known to correlate with increased synchrony of hippocampal theta (8-12 Hz) rhythms to mPFC LFP and unit activity. However, little is understood about how monosynaptic iHC and vHC inputs engage mPFC neural activity along the dorso-ventral axis of the mPFC or how these change with age. To investigate these questions, we delivered 25 individual biphasic electrical pulses (halfwidth: 0.5 ms) ranging in amplitude from 100-600 μA with a 30s interval between pulses across the CA1 layer in iHC and vHC of anesthetized male F344 young (10 months, n = 3) and old (24 months, n = 2) rats. We simultaneously recorded evoked neural activity along the dorsoventral length of the mPFC using Neuropixels 2.0 probes. Recordings were obtained from all 4 shanks spanning 3.84 mm along the DV axis of the mPFC including the prelimbic(PL) and infralimbic(IL) regions (areas 24b and 25). Along the ML axis, the shanks span 720 μm from layer II/III to layer VI. Upon stimulating either the iHC and vHC, we observed that increasing the stimulus amplitude resulted in a decrease in response latency and increase in the magnitude of the LFP response across the mPFC, with a larger relative increase in response to iHC stimulation compared with vHC. We also observed a layer-specific difference in evoked response amplitudes with relatively larger responses in the mPFC layers V/VI compared to layers II/III across all rats and stimulation conditions. Notably, the magnitude of LFP response in the IL regions of the mPFC was larger than in the PL in young rats across stimulation conditions.

In old rats, this increase in response magnitude in the IL region was not observed. The LFP response magnitude to iHC/vHC stimulation also correlated with increased firing of mPFC neurons. The relative increase in the number of mPFC neurons activated by the stimulation was more in the IL region compared to the PL region in young rats, while in old rats, the similar response magnitude resulted in a similar number of neurons activated in both subregions. It appears that the vHC drive to the IL is greater than that to the PL in young rats, and this difference does not emerge in old rats.

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Poster

PSTR366: Aging and Mechanisms of Hippocampal Function

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Topic: H.08. Learning and Memory

Support: McKnight Brain Research Foundation
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Title: Dorsal hippocampal single-unit responses to time, length of string pulled, and trial condition during a novel fine-motor string-pulling behavior

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Abstract: Neural activity in the hippocampus accurately encodes spatiotemporal information during navigation and spatial working memory behaviors, and this activity is believed to underlie the formation and retrieval of episodic memories. While hippocampal single-unit function is largely tied to spatial encoding and retrieval, evidence suggests that hippocampal representations, under the appropriate context and task, can flexibly encode other dimensions such as time and auditory frequency. The present study sought to determine if such representations can extend to ‘length pulled’ in a novel bi-manual string-pulling behavior (Jordan et. al., 2024) where reward was delivered only when a predetermined length of string was pulled. **Methods:** Male Sprague-Dawley rats (N=7) were trained on the string-pulling task that required animals to pull either a short (125cm) or long (250cm) length of string. Each pulling bout was followed by running on a circular two-meter track to retrieve food reward. Neuropixels recordings were acquired from dorsal hippocampal CA1 and CA3 regions (AP: 3.35 ML: 2.8 DV: 8.05). **Results:** Analysis of 1,197 single-units identified subsets of neurons responding to the temporal duration of each pulling episode (18%) with a notably smaller group responding to

the length of string pulled (2%). In addition, 4% of neurons responded to the trial condition (short or long string length). For example, some neurons were only active during the long as opposed to the short pull bouts. Finally, the analysis of randomized probe trials, where the expected reward was not delivered, revealed that 11% of neurons responded at the expected time of reward delivery. These findings are consistent with the idea that the hippocampus tracks the passage of time under these conditions and only minimally tracks string length or distance pulled. These data contribute to growing evidence suggesting that representations in the hippocampus can flexibly adapt to task demands; however, contrary to our prediction that neural responses would reflect string-length or distance pulled, the predominant response was related to time.

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Poster

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UArizona: Office of Diversity and Inclusion
McKnight Brain Research Foundation

Title: CRISPR screening of genes associated with neuronal pentraxin 2 gene expression in human iPSC-derived glutamatergic excitatory neurons

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Abstract: Neuronal pentraxin 2 (NPTX2 or Narp), an immediate early gene enriched at the excitatory synapse of glutamatergic neurons and inhibitory parvalbumin interneurons, is critical in the dynamic regulation of homeostatic scaling of synaptic activity in response to stimuli (Tsui et al., 1996; Xu et al., 2003; Chang et al., 2010). Studies suggest that NPTX2 gene and protein expression is downregulated with aging and greatly reduced at the onset of cognitive impairment in Alzheimer's Disease (Hanson, 2017; Xiao et al., 2017). Glycopeptiforms of NPTX2 have also been implicated in contributing to cognitive resilience in aging populations (Buchman et al.2024). Reprogrammable human induced pluripotent stem cells (hiPSCs) derived from human

adult cells alongside CRISPR gene editing present an innovative approach to investigate these complex cellular mechanisms (Romito and Cobellis., 2015). Brain derived neurotrophic factor (BDNF) signaling has been identified as an upstream bidirectional modulator of expression NPTX2 (Giacobbo et al., 2018; Mariga et al., 2015) but showed low expression levels in hiPSC-derived glutamatergic neurons (bitbio®). In this study, we utilize hiPSC-derived excitatory glutamatergic cortical neurons, generating CRISPR-ready excitatory glutamatergic neurons (bitbio®) to 1) perform a dose-dependent experiment to assess the effects of enriched BDNF in culture medium on NPTX2 mRNA expression over days of treatment; 2) establish a protocol to quantify mRNA levels of NPTX2 using reverse-transcription quantitative polymerase chain reaction (RT-qPCR) readouts and validate a knockdown of NPTX2 in these excitatory glutamatergic neurons; and 3) further develop a protocol for knockout of NPTX2 by optimizing synthetic guide RNA (sgRNA) delivery. Dose-dependent BDNF treatment did not show a significant main effect of BDNF on NPTX2 mRNA expression levels across a 14-day time course experiment in these excitatory neurons. We have established a RT-qPCR method to quantify mRNA levels of NPTX2 with siRNA-knockdown and sgRNA treated neurons compared to control. We plan to further screen other highly correlated target genes with NPTX2 including SCG2, RIMBP2, ARHGEF7, CHGB and TRIM9 through delivery of each sgRNA. The findings here should provide insights into the mechanisms by which additional pathways interact with NPTX2 to produce NPTX2's function in circuits critical for optimal cognitive function.

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Poster

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Topic: H.08. Learning and Memory

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McKnight Brain Research Foundation

Title: Arc mRNA expression pattern in the CA1 subregion of rat hippocampus following spatial behavior

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Abstract: Aging poses significant challenges to cognitive function, particularly in the domain of episodic memory, which relies on the integrity of the hippocampus CA1. Previous studies (Henriksen et al., 2010; Hartzell et al., 2013; Beer et al., 2018; Soltesz and Losonczy, 2018) have addressed functional specialization along the transversal axis of CA1, corresponding to input from the entorhinal cortex. Specifically, the distal CA1 receives projections from the lateral entorhinal cortex (LEC), the proximal CA1 receives projections from the medial entorhinal cortex (MEC), and the medial CA1 receives projections from a combination of LEC and MEC. These projections play a crucial role in processing distinct components of memory along the transversal axis of CA1, resulting in intricate neural representations and diverse behavioral performance. To enhance our understanding of chronological changes within the hippocampus neural network and the impact on cognitive competence, we conducted a comprehensive study investigating the cellular distribution of *Arc* mRNA in the distal, middle, and proximal subregions of the hippocampus CA1 in three distinct age groups (6 months, 15 months, and 23 months) of male Fisher-344 rats. Additionally, within each age group, rats were categorized into three different cognitive performance levels based on their behavior in the spatial version of the Morris watermaze. Our hypothesis was that an effect of aging and level of cognition within age groups would be evident in the cellular distribution of *Arc* mRNA within CA1 subregions. Behaviorally induced *Arc* mRNA expression was investigated by allowing the rats to explore the same environment twice for 5 minutes each, separated by a 20-minute rest period in their home cage. To test whether *Arc* mRNA distribution was consistent with network stability, we first conducted our data analysis in the middle CA1 region. No difference in network stability was noted in young rats with low, average, and high cognitive ability. Old rats, however, exhibited more network stability in the high-performing group compared with the others. The middle-aged rats exhibited a complex network relationship that we are still exploring. Going forward we will examine the data within distal and proximal regions with respect to aging and cognitive status.

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Poster

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Topic: F.03. Stress and the Brain

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Title: Alleviating Effects of Isoquercetin-Ligustrazine Co-polymorph on Cognitive Decline in Hypoxia-Accelerated Alzheimer's Disease

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Abstract: Alzheimer's disease (AD), a prevalent neurodegenerative disorder affecting the elderly population, is commonly co-emergent with obstructive sleep apnea (OSA). Recent reports have indicated that OSA-associated chronic hypoxia could accelerate the progression of AD. However, the cellular stress responses, the roles of the PERK pathways, and relevant pharmacological investigations remain largely elusive. Our research aimed to evaluate the effectiveness of isoquercetin-ligustrazine co-polymorph (ILCP) in alleviating aggravated cognitive deficits in a transgenic model of AD accelerated by chronic hypoxia. In this study, ApoE3/4 transgenic mice underwent four weeks of chronic hypoxia, and relevant hallmarks, including cognitive impairments, oxidative stress levels, β-amyloid protein accumulation, and neuronal apoptosis, were examined. Our findings indicate that chronic hypoxia enhances the activity of the PERK pathway, aggravates neuronal damage, and reduces cognitive abilities. Treatment with ILCP appeared to inhibit the PERK pathway, alleviating oxidative stress, reducing neuronal damage, and preserving synaptic functions. These outcomes suggest that ILCP is potentially a therapeutic option for targeting the overactivated PERK pathway in AD patients with sleep apnea.

Disclosures: X. Long: None. **Y. Yang:** None. **Y. Xie:** None. **J. Shi:** None. **Y. Wang:** None. **X. Xie:** None. **Y. He:** None. **X. Pang:** None. **L. Du:** None.

Poster

PSTR366: Aging and Mechanisms of Hippocampal Function

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.14/V4

Topic: H.08. Learning and Memory

Support: NIA Grant 5R24AG061421
NIA Grant 3P01AG009973

Title: Individual Differences in Cognitive Aging Rodent Datasets (ID-CARD): A shared framework to investigate cognitive reserve and resilience in aging in rodents

Authors: J. A. MCQUAIL[1], C. A. BARNES[2], P. R. RAPP[3], T. C. FOSTER[4], J. F. DISTERHOFT[5], C. C. KACZOROWSKI[6], M. HUENTELMAN[7], J. L. BIZON[8], S. N. BURKE[9], M. GALLAGHER[10], ***A. BRANCH**[11];
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Abstract: Behavioral studies in laboratory rodents have significantly advanced our understanding of neurobiological changes associated with age-related memory loss and diseases, as well as the neural mechanisms that support cognitive reserve and resilience against later-life declines. However, despite the apparent focus on similar cognitive processes across independent studies, there exists substantial variability in the implementation of behavioral testing procedures across different laboratories and research groups. This lack of standardization poses a significant barrier to data sharing, hypothesis generation, and scientific collaboration. The Morris water maze (MWM) is the apparatus used most frequently in rodent behavioral research to assess age- and disease-related cognitive decline. The place-learning version of the MWM taxes explicit learning and memory functions that depend on limbic and cortical systems, which are crucial areas affected by normal aging and neurodegenerative diseases. Notably, the learning and memory patterns observed in aged rodents reflect the diverse spectrum of individual differences seen in humans, offering insights into cognitive reserve and brain maintenance. To address the need for standardized data collection and sharing in this field, we are developing a flexible reporting framework and centralized database tailored for MWM data collected from aging rodents. Numerous laboratories have agreed to contribute substantial datasets, facilitating robust comparisons among aging rodent strains and testing sites over time. Additionally, we plan to expand this resource to include access to biological measures, tissue specimens, and other behavioral or physiological data derived from subjects within the database. Our overarching goal is to establish a shared resource that fosters collaboration and initiatives aimed at advancing the study of cognitive and brain reserve in relevant rodent models of aging and disease, with the ultimate aim of preventing Alzheimer's disease and other late-life neurological disorders.

Disclosures: J.A. McQuail: None. **C.A. Barnes:** None. **P.R. Rapp:** None. **T.C. Foster:** None. **J.F. Disterhoft:** None. **C.C. Kaczorowski:** None. **M. Huentelman:** None. **J.L. Bizon:** None. **S.N. Burke:** None. **M. Gallagher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AgeneBio Incorporated. **A. Branch:** None.

Poster

PSTR366: Aging and Mechanisms of Hippocampal Function

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.15/V5

Topic: H.08. Learning and Memory

Support: CHESS Région Nouvelle Aquitaine Exomarquage
ANR JCJC ExoNutriAge
JPND Solid
Digit-BIO INRAE Dynamic

Title: Sex difference in cognitive deficits and hippocampal alterations induced by n-3 polyunsaturated fatty acid deficiency

Authors: *I. MARNIQUET, F. CRESPO, L. BARRY-CARROLL, H. V. LAD, S. LAYÉ, J.-C. DELPECH;
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Abstract: The rise in the elderly population is leading to an increase in the number of people suffering from cognitive decline, causing major socio-economic stress on the healthcare system. Among the environmental factors, nutrition and in particular polyunsaturated fatty acids (PUFAs) appear to be crucial. Dietary changes over the last few decades have led to an increase in the number of people deficient in n-3 PUFAs, in favor of an increase in n-6 PUFAs. This n-6 PUFA/n-3 PUFA disbalance is linked to an increased risk of cognitive alterations. Preclinical studies have shown that early deficiency leads to impaired working memory at weaning in males, and that supplementation with n-3 PUFAs in old animals restores their working memory. However, the cognitive dimensions affected and the underlying neurobiological mechanisms remain poorly understood. I am interested in the cognitive changes in the subject in relation to his n-3 PUFA intake, and the mechanisms involved as a function of sex. To do this, I use a nutritional approach involving gestational deficiency in n-3 PUFAs in C57Bl6/J male and female mice. In adulthood (3-month-old), I am studying multiple behavioral dimensions such as anxiety, spatial working memory and associative spatial and temporal memories. Spatial working memory tested with object location memory is impaired in deficient n-3 PUFA of both sexes (N=28-32; 3 cohorts). We used delayed fear conditioning to assess contextual memory at 24 hour and 10 days. Our results show an impaired contextual memory at 24h in deficient females (N=20; 2 cohorts) and only after 10 days in males (N=16-18; 2 cohorts). Anxiety tested in elevated plus maze and open field was not increased in deficient animals (N=28-32; 3 cohorts). Electrophysiological recording in whole cell patch clamp of pyramidal neuron of the dorsal CA1 were performed to assess neuronal excitability (N=6). In deficient animals, those neurons were more excitable but with an increase resting membrane potential in males and a decrease action potential threshold and rheobase in females. We characterized kinases activity of the hippocampus (N=8) with PAMGENE microarray. Kinases involved in synaptic organization were increased in female mice and decreased in male animals. This was linked to a decrease in vesicular glutamate transport 1 (VGlut1) and postsynaptic density protein 95 (PSD-95) colocalization in males but not females. My results indicate that early n-3 PUFA deficiency alters hippocampal-dependent memories in both sexes, linked to sex-dependent change in neuronal excitability. These results may pave the way to better understand sex-dependent cognitive alterations due to abnormal nutritional intake.

Disclosures: I. Marniquet: None. **F. Crespo:** None. **L. Barry-Carroll:** None. **H.V. Lad:** None. **S. Layé:** None. **J. Delpech:** None.

Poster

PSTR366: Aging and Mechanisms of Hippocampal Function

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR366.16/V6

Topic: H.08. Learning and Memory

Support: R01-AG048907
R01-AG049464

Title: Identification of novel activity-related transcripts using laser capture microdissection and RNA sequencing

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Abstract: Activity-regulated genes (ARGs) are genetic regions that respond to neuronal cell activity changes. ARGs are important in neuronal health and disease, and play a central role in memory formation and plasticity. Arc (activity regulated cytoskeleton associated protein) is a prototypical ARG wherein neuronal depolarization results in increased transcription as well as a time-related differential compartmentalization of Arc RNA from the neuronal soma into the dendrites. To identify novel ARGs we laser capture microdissected four hippocampus cell compartments in the CA1, CA3b, CA2, and dentate gyrus regions including their soma and dendritic fields individually. The experimental cohort was comprised of six-month-old F-344 rats at multiple time points (10, 30 min, 1, 2, 4, and 24 hours; n=6 per time point) following maximal electroconvulsive shock (MECS). We used RNA sequencing and performed differential expression analysis to identify transcripts that were altered by MECS both in quantity and by compartment (soma vs. neuropil). We found eight novel activity-regulated genes that exhibited Arc-like transcriptional response profiles characterized by the following aspects; transcripts were (1) not differentially compartmentalized at rest, (2) significantly increased in expression in the soma compartment before the neuropil, and (3) not previously reported as an ARG. We validated one of these novel ARGs, Trib 1 (Tribbles Pseudokinase 1), using chromogenic in situ hybridization (RNAScope; ACD Bio). Trib1 expression was quantitated by pixel intensity analysis of images captured by the Aperio ImageScope in the same soma and neuropil regions of the hippocampus. The RNAScope results confirmed our RNA-sequencing findings and demonstrated that Trib1 exhibits both a transcriptional and compartmentalization response similar to Arc, positioning Trib 1 as a novel activity-regulated transcript. Trib1 is a pseudokinase that plays a role as a molecular scaffold to initiate degradation of its substrates via the ubiquitin proteasome system. One such substrate is C/EBPalpha; a member of a family of proteins with known roles in cognitive function. Trib1 has also been found to interact with and regulate various MAP kinase family members. Based on our observations, we propose that Trib1 is a new activity-regulated transcript and encourage future evaluations of Trib1 and the role it may play in activity-regulated neural cell physiology.

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Poster

PSTR367: Hippocampal Circuits in Cognitive Tasks

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.01/V7

Topic: H.08. Learning and Memory

Support: NIH R01MH129294
NIH R01MH130367

Title: Hypothalamic regulation of hippocampal CA1 interneurons by supramammillary nucleus

Authors: Y.-Q. JIANG, D. K. LEE, M. LI, ***Q. SUN**;
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Abstract: The hypothalamic supramammillary nucleus (SuM) projects heavily to the hippocampus to regulate hippocampal activity and plasticity. Although the role of SuM-dentate gyrus (DG) and SuM-CA2 pathways in hippocampal-dependent behaviors has been extensively studied, whether the SuM projects to CA1, the main hippocampal output region, is unknown. Here, we report a novel glutamatergic pathway from SuM that selectively excites CA1 interneurons in the border of stratum radiatum (SR) and stratum lacunosum-moleculare (SLM). We find that the SuM projects selectively to a narrow band in CA1 SR/SLM border and makes monosynaptic connections onto SR/SLM interneurons, including vasoactive intestinal peptide-expressing (VIP+) and neuron-derived neurotrophic factor-expressing (NDNF+) cells, but completely avoids making monosynaptic contacts with CA1 pyramidal neurons (PNs), parvalbumin-expressing (PV+), or somatostatin-expressing (SOM+) cells. Moreover, SuM activation drives spikes in most SR/SLM interneurons to suppresses CA1 PN excitability. Taken together, our findings demonstrate SuM can directly regulate CA1, bypassing CA2, CA3, and DG.

Disclosures: Y. Jiang: None. **D.K. Lee:** None. **M. Li:** None. **Q. Sun:** None.

Poster

PSTR367: Hippocampal Circuits in Cognitive Tasks

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Program #/Poster #: PSTR367.02/V8

Topic: H.08. Learning and Memory

Support: NIH Grant F31-NS127417
NIH Grant R01-NS104071
University of Minnesota's MnDRIVE
McKnight Land Grant Professorship

Title: Hippocampal inhibitory neurons target burst-firing cells of the supramammillary area

Authors: *L. GLASSBURN[1], E. MARRON[2], E. I. KROOK-MAGNUSON[3];
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Abstract: The supramammillary area (SuM) projects directly to the hippocampus, and has been shown to impact hippocampal theta oscillations, spatial and social processing, and memory. Different populations of SuM neurons are believed to project to different areas within the hippocampus, including the dorsal versus ventral dentate gyrus. Less is known about hippocampal influence on the SuM. Previous work established that a neuronal nitric oxide synthase (nNOS)-expressing inhibitory population, termed LINCs, projects from the hippocampus to the SuM. Using fluorogold retrograde tracing, we have found that inhibitory cells from across the dorsoventral axis and across hippocampal subregions project to the SuM, of which LINCs is one subpopulation. To examine the connectivity of these projections, we expressed channelrhodopsin in either ventral or dorsal hippocampal inhibitory neurons, and performed whole-cell patch clamp recordings from retrogradely labeled SuM neurons projecting to the dorsal dentate gyrus ("$SuM_{\rightarrow dorsalDG}$") or the ventral dentate gyrus ("$SuM_{\rightarrow ventralDG}$"). We find that $SuM_{\rightarrow dorsalDG}$ cells can receive inhibitory input from the dorsal hippocampus (1 of 6 cells, 17%, amplitude 4 pA) or from the ventral hippocampus (6 of 22 cells, 22%, average amplitude 42.6 +/-91.2 pA), arguing against a simple feedback loop. A similar proportion of $SuM_{\rightarrow ventralDG}$ cells were innervated by ventral hippocampus (3 of 18 cells, 14%, average amplitude 33.1+/-1.7 pA). Overall, patched DG-projecting SuM cells were sparsely innervated, as were other patched unlabeled SuM cells (8 of 81 cells, 10%, average amplitude 25.5pA+/-33.43 pA). This relatively low connectivity in SuM cells, and connectivity across projection-defined groups, suggests that specific subpopulations (not defined by their dorsal versus ventral DG projection targets) may be selectively receiving inputs. We therefore examined the firing properties of patched SuM cells, and how that may relate to inhibitory hippocampal inputs. We found that burst-firing cells of the SuM were disproportionately innervated by hippocampal inhibitory neurons compared to non-burst firing cells (6 of 13, 46%, burst-firing cells vs. 12 of 127, 9%, non-burst firing cells innervated, $p<0.001$, chi square). Collectively, our data indicates that hippocampal inhibitory projections disproportionately target supramammillary burst-firing cells and innervate both $SuM_{\rightarrow dorsalDG}$ and $SuM_{\rightarrow ventralDG}$ projecting populations.

Disclosures: L. Glassburn: None. **E. Marron:** None. **E.I. Krook-Magnuson:** None.

Poster

PSTR367: Hippocampal Circuits in Cognitive Tasks

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.03/V9

Topic: G.05. Mood Disorders

Support: NIH Grant MH13432
NIH Grant GM142521
NIH Grant MH111604

Title: Androgen receptor dependent regulation of projection-specific hippocampal neuronal excitability

Authors: *C. SUGIMOTO[1], A. L. EAGLE[2], R. M. BASTLE[3], I. S. MAZE[3], A. J. ROBISON[1]; [1]Dept. of Physiol., Michigan State Univ., East Lansing, MI; [2]Dept. of Neurosci., Univ. of Texas at Dallas, Richardson, TX; [3]Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, Ossining, NY

Abstract: Major depressive disorder (MDD) is highly prevalent and has a complex multifactorial etiology, with stress vulnerability emerging as a critical risk factor. MDD prevalence is almost double in women compared to men, but the biological basis of this sex difference is not understood. Additionally, roughly half of MDD patients do not respond to existing treatments, and thus there is an urgent need to understand MDD's cellular and the molecular mechanisms to develop new therapeutic strategies. MDD is associated with abnormalities of the brain's reward circuitry, and ventral hippocampal (vHPC) projections to the nucleus accumbens (NAc; vHPC-NAc) have been implicated in stress-induced susceptibility to anhedonia in male mice. However, despite the higher prevalence of MDD in females, studies that include both male and female subjects are lacking. Our lab used subchronic variable stress (SCVS), which induces an anhedonia-like phenotype in female mice but not males, to mechanistically investigate the sex differences in stress-induced anhedonia. We found that female mice have increased basal vHPC-NAc intrinsic excitability compared to males, and that this directly drives anhedonia-like behavior following SCVS. Moreover, vHPC-NAc circuit excitability is reduced by adult testosterone, but the mechanisms by which androgen receptors (AR) regulate this excitability remain unknown. We used *ex vivo* whole cell slice electrophysiology on WT- and conditional AR knockout (AR cKO)-L10GFP mice to examine the role of AR in vHPC-NAc excitability in male and female mice. We found that removing AR from vHPC-NAc increased excitability in males. Moreover, the increased circuit excitability in females compared to males was dependent on non-aromatized androgens, and conditionally knocking out ARs in the vHPC-NAc circuit reversed these effects. Action potential waveform analysis suggested that potassium and calcium channels may play a key role in this excitability change. Therefore, we used translating ribosome affinity purification sequencing (TRAP-seq) to examine downstream targets of AR and observed changes in expression of multiple ion channels and signaling pathways which drive sex-specific behaviors and vulnerability to stress. Furthermore, we investigated the AR signaling pathways necessary to drive changes in vHPC-NAc excitability by using pathway-specific AR knockouts. ARs can operate via the canonical pathway of binding DNA to alter gene expression or through non-canonical membrane-bound signaling in the cytosol, and we hypothesize ARs reduce excitability of vHPC-NAc neurons through directly changing gene expression in the nucleus.

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Poster

PSTR367: Hippocampal Circuits in Cognitive Tasks

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Topic: G.05. Mood Disorders

Support: NIH Grant MH13432
NIH Grant GM142521
NIH Grant MH111604
MSU Honors College Hymen and Miriam Stein Scholarship

Title: Validation of androgen receptor signaling pathway-specific knockout mice in ventral hippocampal projection neurons

Authors: *G. A. STYS, C. SUGIMOTO, A. J. ROBISON;
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Abstract: Major depressive disorder (MDD) is a highly prevalent psychological disorder that is more prevalent in women than men. Over half of patients do not fully respond to current treatments, underscoring the urgent need for a better understanding of the molecular mechanisms underlying the disease. Previous studies have implicated a role of disregulation of brain reward circuitry in MDD, including the ventral hippocampus (vHPC, responsible for emotional memory) and the nucleus accumbens (NAc, regulates motivation and reward seeking). vHPC projections to the NAc (vHPC-NAc) have been implicated in stress-induced susceptibility to anhedonia in mice. Our lab used subchronic variable stress (SCVS), to induce an anhedonia-like phenotype in female mice but not males, mimicking the prevalence of MDD in female patients, and found females mice have increased basal vHPC-NAc circuit excitability compared to males, and this drives susceptibility to SCVS-induced anhedonia. We also showed that this vHPC-NAc circuit excitability is reduced by adult testosterone signaling through androgen receptors (ARs) on vHPC neurons, but the signaling pathway by which ARs regulate this excitability is unknown. ARs can function either by the classical (nuclear) pathway of binding to DNA to modify gene expression, or through non-classical membrane-bound signaling within the cytosol. We used two transgenic mouse lines, the nuclear only AR (NOAR), and membrane one AR (MOAR) mice to selectively isolate the AR signaling pathways. To validate the NOAR and MOAR mouse lines, we activated ARs in a slice preparation of mouse hippocampus using dihydrotestosterone and then used immunohistochemistry (IHC) to stain for phosphorylated extracellular regulated kinase (pERK) in the vHPC-NAc projecting neurons. pERK is a useful marker of the membrane pathway, as it is produced by signaling cascades downstream of membrane-bound AR. We also stained for the AR itself to verify its location (nuclear vs cytosolic) in the cells in each mouse line. Fluorescent microscopy was utilized to visualize the pERK and GFP colocalization in vHPC-NAc neurons and quantify expression levels. We found normal pERK colocalization in the vHPC-NAc neurons in both the wild type and MOAR mice and reduced pERK colocalization in the NOAR mice, validating these lines for use in brain AR manipulation. Further exploration of the signaling pathways of the AR will increase our understanding of the sex differences observed in MDD, and why women are disproportionately affected by the disorder, eventually allowing better targeted treatments and therapies for patients of both sexes.

Disclosures: G.A. Stys: None. **C. Sugimoto:** None. **A.J. Robison:** None.

Poster

PSTR367: Hippocampal Circuits in Cognitive Tasks

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.05/V11

Topic: H.08. Learning and Memory

Support: DA034231
DA044939

Title: Ccr5 inhibition improves spatial learning and memory performance in a non-infectious model of hiv-associated neurocognitive disorder: sex difference in outcomes

Authors: *C. SIMONS[1], S. KIM[1], A. BOAKYE-AGYEI[1], Y.-K. K. HAHN[1], S. NASS[2], K. HAUSER[2,1,3], P. KNAPP[1,2,3];
[1]Anat. and Neurobio., [2]Pharmacol. and Toxicology, [3]Inst. for Drug and Alcohol Studies, Virginia Commonwealth Univ., Richmond, VA

Abstract: People with HIV (PWH) continue to experience HIV-associated neurocognitive disorders (HAND), even though combination antiretroviral therapy (cART) successfully suppresses HIV replication. Among the causes for this are direct neurotoxic and inflammatory effects of several viral proteins, including HIV-1 transactivator of transcription (Tat). Although there has been a shift from severe to milder forms of HAND, roughly 50% of PWH develop cognitive, motor, and mood problems that reduce quality of life. Neuroinflammation has been shown to contribute to the development of HAND, so targeting an inflammatory pathway could be a key therapeutic approach. C-C chemokine 5 (CCR5) acts as a chemoattractant to aid in the migration of cells to areas of infection, thus activating an inflammatory response. CCR5 also plays an important role in the life cycle of HIV as a co-receptor for viral entry into CD4+ target cells. CCR5 has also been implicated in cognitive function unrelated to HIV infection, as CCR5 inhibition has been shown to improve learning and memory. (Joy *et al.* 2019; Zhou *et al.* 2016; Frank *et al.* 2018; Shen *et al*. 2022). To test whether CCR5 is involved in cognitive changes in HAND apart from its role in viral entry, we used a non-infectious, transgenic model in which HIV-1 Tat is inducibly expressed. 2-3-mo old mice were placed on a diet containing doxycycline to induce Tat expression for 8-wk. Maraviroc (MVC), a CCR5 antagonist, was given for the last 10 d by oral gavage. In males (n=11-12), but not females (n=13-15), we saw Tat-mediated deficits in the Barnes maze test of spatial learning and memory. These deficits were reversed by MVC, suggesting an integral role for CCR5 in HIV-induced spatial learning dysfunction. Tat-mediated deficits were not found in either novel object recognition or contextual fear conditioning (n=15-17). However, MVC did enhance memory consolidation in a contextual fear conditioning paradigm in male Tat- mice. It is widely accepted that certain brain regions are more susceptible to HIV injury (Corrêa et al., 2016; Israel et al., 2019) and we saw that cognitive dysfunction varied based on sex and the test performed. Since brain-derived neurotrophic factor (BDNF) plays a key role in the plasticity underlying learning/memory and is reduced in people with HAND (Bachis et al. 2012), we measured mature BDNF and proBDNF in an ELISA assay. Male Tat+ mice tested in the Barnes maze had a higher mBDNF/proBDNF ratio

(neuroprotective) when treated with MVC, further supporting CCR5's role in mediating cognitive ability and function in HAND.

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Poster

PSTR367: Hippocampal Circuits in Cognitive Tasks

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.06/V12

Topic: H.08. Learning and Memory

Support: R01MH129294
R01MH130367

Title: Top-down control of subcortical activity by dual-projecting hippocampal long-range inhibition

Authors: *J. KINNEY[1,2], M. ZHOU[3], Y.-Q. JIANG[3], D. LEE[3], H. WANG[3], M. LI[3], H. L. ROBINSON[4], A. OLIVA[4], Q. SUN[3];
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Abstract: SFN Abstract – Jessica KinneyTitle: Top-down control of subcortical activity by dual-projecting hippocampal long-range inhibitionAuthors: Kinney JL[1], Zhou M[1], Jiang YQ[1], Lee D[1], Wang H[1], Li M[1], Robinson HL[2], Oliva A[2], Sun Q[1]. **Affiliations:** [1]Department of Neurosciences, School of Medicine, Case Western Reserve University [2] Department of Neurobiology and Behavior, Cornell University
Area CA3 in the hippocampus is essential for intra-hippocampal information processing by linking dentate gyrus to CA1 via classic entorhinal cortex◊dentate gyrus◊CA3◊CA1 trisynaptic pathway. By comparison, little is known about top-down control of subcortical activity by CA3 long-range inhibition. Here we identified a novel somatostatin-expressing (SOM+) dual-projecting inhibitory pathway from CA3 to medial septum (MS) and supramammillary nucleus (SuM) – two key regions important for theta oscillations. We used cell-type and pathway specific anterograde and retrograde tracing to show that the same CA3 SOM+ neurons project to both MS and SuM. Ex vivo patch-clamp recordings assisted by channelrhodopsin-2 (ChR2) further demonstrate that this long-range inhibition preferentially target fast-spiking (presumptive GABAergic) and cluster firing (presumptive glutamatergic) neurons in MS, while preferentially suppressing fast-spiking (presumptive GABAergic) neurons in SuM. Moreover, optical stimulation of CA3 SOM+ terminals at theta frequencies entrain theta firing of the postsynaptic neurons in MS and SuM both in vitro and in vivo. Given that the MS, SuM, and hippocampus are strongly involved in theta oscillations, we propose that this top-down inhibitory projection is

ideally positioned to coordinate and synchronize hippocampal-subcortical rhythmic activity, such as theta oscillations.

Disclosures: J. Kinney: None. **M. Zhou:** None. **Y. Jiang:** None. **D. Lee:** None. **H. Wang:** None. **M. Li:** None. **H.L. Robinson:** None. **A. Oliva:** None. **Q. Sun:** None.

Poster

PSTR367: Hippocampal Circuits in Cognitive Tasks

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Program #/Poster #: PSTR367.07/V13

Topic: H.08. Learning and Memory

Support: R01MH129294
R01MH130367

Title: A Circuit from Basolateral Amygdala to Hippocampal CA3 Regulates Social Behavior

Authors: *M. LI[1], J. KINNEY[2], Q. SUN[2];
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Abstract: The hippocampal CA3 region plays a crucial role in learning and memory. The defining features of CA3 include its extensive recurrent excitatory system and powerful mossy fiber inputs from dentate gyrus (DG), which have been extensively studied. Yet, aside from entorhinal cortex, the functional connections to CA3 from extra-hippocampal regions remain largely unknown. Here we report a monosynaptic glutamatergic pathway from a small group of basolateral amygdala (BLA) neurons that selectively innervates ventral CA3 and plays an important role in social behavior. We found that CA3-projecting BLA neurons were topographically clustered in BLA adjacent to the midline, selectively innervated basal dendrites of ventral CA3a/b (close to CA1) and were nearly devoid of CA3c (next to DG). Using Channelrhodopsin2 (ChR2)-assisted ex vivo patch-clamp recording, we further showed that BLA selectively excited regular-spiking CA3a/b neurons in the ventral hippocampus that contained thorny excrescences, only weakly excited CA2 neurons (an order of magnitude smaller), and completely avoided athorny bursting-firing CA3 neurons. Moreover, BLA-CA3 synapses were glutamatergic and displayed robust temporal summation in responses to repetitive light stimulation. Finally, chemogenetic suppression of CA3-projecting BLA neurons enhanced social interaction and impaired social memory. Taken together, our results identified a novel circuit from BLA to ventral CA3 that can regulate social behavior.

Disclosures: M. Li: None. **J. Kinney:** None. **Q. Sun:** None.

Poster

PSTR367: Hippocampal Circuits in Cognitive Tasks

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR367.08/V14

Topic: H.08. Learning and Memory

Support: STI2030-Major Projects (2022ZD0204600)

Title: Dynamic neural communication during rapid speech learning from a single exposure

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Abstract: Dynamic neural communication during rapid speech learning from a single exposure
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Disclosures Meiyun Wu: None. Hui Zhang: None. Jinhong Li: None. Yu-Xuan Zhang: None.
AbstractsMost autobiographic memories of humans are formed after a single exposure, yet the underlying neural mechanisms remain elusive. We recorded iEEG data from 30 epileptic patients (mean age:10.1 years, 11 females) during two repeated trials of natural speech, with a total of 556 electrodes mapped onto seven canonical resting-state networks. Significant power changes of low (1 to 7 Hz) - and high (80 to 200 Hz)-frequency local field potentials between the first and second trials were found in the auditory cortex, hippocampus, amygdala, default mode network (DMN) and somatomotor regions, suggesting that single-trial learning involves large scale brain networks. Interestingly, cross-correlation analyses revealed a directional reversal of low-frequency information flow between the auditory cortex and the hippocampus in this process: upon the first exposure neural activities of the auditory cortex lead and predict those of the hippocampus, and upon the second hearing they lag behind and are predicted by those of the hippocampus. In addition, the mutual information between the auditory cortex and the hippocampus during the second exposure was positively correlated with the frequency of recalled words. These results suggest that the interplay between auditory cortical and hippocampal dynamics may play a critical role in single-trial memory formation of natural speech.

Disclosures: M. Wu: None. **Y. Zhang:** None.

Poster

PSTR367: Hippocampal Circuits in Cognitive Tasks

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the Key R&D Program of Zhejiang (2021C03003, 2022C03029, 2021C03050, 2022R52033)
the National Natural Science Foundation of China (31371001)

Title: Amygdala engages non-emotional multi-item working memory maintenance through amygdala-hippocampus interaction

Authors: *C. LI[1], Y. PENG[1], R. WANG[2], Y. NING[3], Y. MA[1], D. WU[1], W. CHEN[1], S. ZHANG[4];
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Abstract: The maintenance process of holding information in working memory (WM) is an active one that requires neural activity within and between regions. The human amygdala (AMY) and hippocampus (HPC) have been known to play crucial roles in emotional WM processing. Although human electrophysiological studies have made remarkable progress in revealing that HPC supports multi-item maintenance in a load-dependent manner, the characteristics of AMY and the circuit-level mechanisms underpinning AMY-HPC interactions remain largely unexplored. To address these issues, we employed intracranial EEG recordings from AMY and HPC in nine epileptic patients to investigate intra-regional neural representations and inter-regional communications during maintenance under different non-emotional WM loads. We characterized the properties of low-frequency oscillations (theta=3-8 Hz and alpha=8-13 Hz) and intra-regional theta-gamma (gamma=30-100 Hz) phase-amplitude coupling (PAC) during WM maintenance in each region. To quantify cross-regional connectivity between the AMY and the HPC, we assessed directional and non-directional metrics, including Weighted Phase Lag Index (wPLI), Granger causality (GC), Phase Slope Index (PSI), cross-regional theta-gamma PAC. Our results show that high load enhances low-frequency power and intra-regional theta-gamma PAC in AMY and HPC. On the network level, high load elicits an increase in the strength of the modulation of HPC theta phase entraining AMY gamma amplitude. Furthermore, high load elevates AMY-anterior HPC (aHPC) theta phase synchrony and directional connectivity strength, with the direction from aHPC to AMY. Conversely, posterior HPC (pHPC)-AMY synchrony is not affected by WM load. The above connectivity characteristics occurred exclusively during the correct trials. Our findings support the idea that the AMY not only serves emotion processing, but also contributes to higher cognition, especially neutral WM. This study underscores the importance of AMY in non-emotional memory tasks and provides a novel insight into the neurophysiological basis of human AMY and its interaction with HPC during WM maintenance.

Disclosures: C. Li: None. **Y. Peng:** None. **R. Wang:** None. **Y. Ning:** None. **Y. Ma:** None. **D. Wu:** None. **W. Chen:** None. **S. Zhang:** None.

Poster

PSTR367: Hippocampal Circuits in Cognitive Tasks

Location: MCP Hall A

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Topic: G.04. Emotion

Support: the National Natural Science Foundation of China（No.62077010）

Title: Concentric encoding of generalizable 2D emotion representations in human hippocampal-neocortical networks

Authors: *S. WU[1], H. CAO[1], H. ZHAO[1], S. QIN[2];
[1]Beijing Normal Univ., Beijing, China; [2]Fac. of Psychology, Stanford Univ., Beijing, China

Abstract: Human emotional systems are adept at constructing and generalizing memories with minimum threat experience into unfamiliar contexts and enable adaptive behaviors. The theory of constructed emotion suggests that instances of emotion are constructed predictively and often accompanied with multidimensional psychophysiological features. By this theory, when constructing an emotion representation, one might anchor to a specific landmark, like the egocentric encoding. While recent studies showed that cognitive maps enable flexible inference with a grid-cell coding. However, little is known how emotional instances are constructed from multidimensional sources and generalized into unfamiliar context. To address this question, we used a 2D-fear learning paradigm where shock intensities and probabilities elicited fear and anxiety responses, respectively. We used fMRI with an avoidance choice task, requiring subjects to combine shock intensity and probability. Before the task, subjects learned the relationship between shock intensities (1-5) and the devil's horn length, as well as the relationship between shock probabilities (1/6 to 5/6) and the devil's leg length. In the task, subjects chose the less avoided devil. Behavioral results showed that choices between similar devils had longer response times($p<0.001$). The distance effect confirms the construction of the emotional space. To test the grid-like coding, we used a General Linear Model with $\sin6\theta$ and $\cos6\theta$ as regressors and found no activation in the entorhinal cortex ($p>0.05$, FWE corrected at cluster level with $q = 0.05$). Further analysis with representational similarity analysis in the hippocampus, entorhinal cortex, and intraparietal sulcus, followed by multidimensional scaling. Emotional space mapped as concentric circles centered around the devil with medium intensity (3) and probability (1/2). Other devils are uniformly distributed around, with each circle's radius calculated by the square root of the sum of the squared differences in shock intensity and probability from the central devil. Confirmatory analyses with concentric circles model RDM and neural RDM showed strong correspondence ($P<0.001$), unlike the grid-cell coding model RDM($P>0.05$). Our findings suggest that concentric representation could organize embodied emotional space.

Disclosures: S. Wu: None. **H. cao:** None. **H. zhao:** None. **S. Qin:** None.

Poster

PSTR368: Oscillations Underlying Memory Functions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.01/V16

Topic: H.08. Learning and Memory

Support: JSPS Research Fellowships for Young Scientists, 24KJ1151
JST SPRING, Grant Number JPMJSP2104
JST Moonshot R&D Grant Number JPMJMS2292

Title: The consistency of the EEG dynamics related to perceptual learning

Authors: *Y. GOTO[1,2], M. HAGIHARA[1,2], K. KITAJO[1,2];
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Abstract: The neural activity to an identical input is known to show inconsistency caused by variabilities at various spatial scales from the single-cell spikes to scalp electroencephalograms (EEG). Furthermore, from the view of the nonlinear dynamical systems theory, nonlinear systems, such as the brain, are known to have sensitivity to initial conditions. However, despite these inherent inconsistencies in the nervous system, our perceptual and motor experiences somehow remain relatively consistent. Recent experimental studies have suggested that neural responses become more consistent when exposed to repeatedly presented stimuli, enhancing perceptual consistency in an implicit and unsupervised manner. Additionally, our neural network simulation study has reported that the plasticity in neural networks reduces the sensitivity to initial conditions and promotes the consistency to stimulus patterns experienced multiple times—we call this "*selective consistency*". Furthermore, we demonstrated that the ability of networks to acquire selective consistency is strongly influenced by the network's complexity, and is maximized at the edge of chaos, slightly leaning towards chaos. To test the hypothesis of selective consistency and its neural correlates, we conducted a human auditory experimental study using the noise repetition-detection (NRD) task and scalp EEG recordings. Twenty-four naïve participants listened to white noise sequences and were required to detect the sequences consisting of temporal repetition (Repeated noise; RN). Without the participants' realization, some of the stimuli were presented multiple times within experimental blocks (Referenced repeated noise; RefRN). Behavioral performance and the inter-trial phase coherence of temporal delta EEG were higher for RefRN than RN—they acquired selective consistency for RefRN. Additionally, we found that the behavioral performance strongly depended on the brain state before the repetitive segments regardless of the stimuli types (RefRN/RN). These findings suggest that neural consistency has a certain degree of sensitivity to initial conditions, which is overcome through repetitive experience, as predicted by our theoretical study. Additionally, these relationships are stronger in neurotypical individuals with high ADHD tendencies consistent with recent experimental studies suggesting that individuals with strong ADHD tendencies exhibited higher complexity in neural networks' structure and activities. This correlation also validates our theoretical predictions regarding the relationship between the edge of chaos and selective consistency.

Disclosures: Y. Goto: None. **M. Hagihara:** None. **K. Kitajo:** None.

Poster

PSTR368: Oscillations Underlying Memory Functions

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.02/V17

Topic: H.08. Learning and Memory

Support: NIH Grant R01 MH116500

Title: Examining the origin of visually-evoked theta oscillations

Authors: *M. ZIMMERMAN[1], S. T. KISSINGER[1], A. A. CHUBYKIN[2];
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Abstract: Our brains are continuously deciphering what sort of action needs to be taken given the situation as we interact with the world around us. One line of thought proposes that prediction errors, when our internal perception of the environment around us differs from the sensory input we receive, drive much of the brain's focus. At the core of this theory is a separation of stimuli into one of two categories; novel or familiar, better termed as experience. In mice, visual experienceis shown to give rise to visually evoked theta (4-8 Hz) oscillations in the primary visual cortex (V1). Recent work from our lab has shown the presence of these oscillations outside of V1 in higher-visual areas (HVAs), which are synchronized with V1 in a context-dependent manner. It remains unclear, however, where these unique oscillatory dynamics originate; whether from the cortex, thalamus, hippocampus, or other-memory related brain regions. To address this, we conducted paired extracellular silicon probe recordings in two visual thalamic nuclei (dorsal lateral geniculate nucleus, dLGN, andlateral posterior thalamus, LP), the retrosplenial cortex (RSC), which is a non-visual cortical area directly connected with V1, and the hippocampus (HPC), which is widely known to be involved in memory encoding and retention. We find that both thalamic nuclei show no oscillatory activity, however, both RSC and the HPC demonstrate a sparse population of neurons with theta oscillations, with the RSC activity temporally delayed. To determine if the activity in the HPC was interacting with V1 to associate the familiarity, we performed hippocampal lesioning and found that it did not modify the activity in V1. These results suggest two things; first, the oscillations are primarily originating in V1 and not initially in thalamic regions, and second, there is little to no interaction between the theta oscillations in V1 and the HPC in response to known, familiar stimuli. Overall, this work sheds light on the purpose of these visually-evoked theta oscillations and determines the role they play in cross-brain relay of information for memory encoding and retention.

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Poster

PSTR368: Oscillations Underlying Memory Functions

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Program #/Poster #: PSTR368.03/V18

Topic: H.08. Learning and Memory

Title: Bla-mpfc circuit dynamics during retrieval and suppression of aversive memories

Authors: *S. A. MERLO[1,2,3], E. MERLO[4], M. E. PEDREIRA[1], M. A. BELLUSCIO[2,3]; [1]Inst. de Fisiología, Biología Mol. y Neurociencias (IFIByNE - CONICET), Buenos Aires, Argentina; [2]Univ. de Buenos Aires, CONICET, Inst. de Fisiología y Biofísica Bernardo Houssay, Grupo de Neurociencia de Sistemas, Lab. Bases Neuronales del Comportamiento, Buenos Aires, Argentina; [3]Univ. de Buenos Aires, Facultad de Medicina, Dept. de Ciencias Fisiológicas, Buenos Aires, Argentina; [4]Sch. of Psychology, Univ. of Sussex, Falmer, United Kingdom

Abstract: The basolateral amygdala (BLA) and the medial prefrontal cortex (mPFC) are key for encoding and retrieval of fear memories. Distinctive BLA neuronal subpopulations are differentially activated by fear memory retrieval, and extinction. Fear memory retrieval activates so called ‘fear neurons’, whereas fear memory extinction activates a different set of BLA neurons, so called ‘extinction neurons’, and silences the ‘fear neurons’. The mPFC is differentially connected to the BLA by different subregions. The prelimbic (PL) region connects to the BLA ‘fear neurons’, and is involved in fear memory expression. The infralimbic (IL) region connects with the BLA ‘extinction neurons’, and is required for fear memory extinction with a mPFC-to-BLA directionality of information. Here, we used rats to record local field potentials (LFP) in BLA and mPFC during fear memory acquisition, retrieval, and extinction. Since LFP is a proxy for population-based neural activity, we explore the dynamics of different oscillation rhythms and the synchronization between PL, IL, and BLA. In particular, we studied how the transition between fear memory retrieval and extinction occurs, in terms of BLA-mPFC network dynamics when the animal's conditioned response is gradually reduced by repeated presentations of the fear cue without negative consequences. Our results show that both BLA and mPFC are involved in valence encoding, as evidenced by specific oscillatory activity patterns. Negative valence encoding is disrupted by memory extinction, and replaced by a new encoding of the new extinction memory trace. Moreover, synchronization between the BLA and the mPFC emerges as a key mechanism in this encoding process. These findings contribute to a deeper understanding of the neural mechanisms underlying the encoding and extinction of negative valence memories, underscoring the importance of the BLA-mPFC interplay in this process.

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Poster

PSTR368: Oscillations Underlying Memory Functions

Location: MCP Hall A

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Program #/Poster #: PSTR368.04/V19

Topic: H.08. Learning and Memory

Support: NSF DGE-1839285

Title: Decoding trial-specific content using CA1 local field potential activity

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Abstract: The hippocampus is a critical hub in the network of brain structures supporting memory for sequences of events. To investigate the underlying neural mechanisms, the current standard is to decode the information contained in the spiking activity of hippocampal ensembles. While this approach has been successful, it is also technically challenging and may result in unpredictable yields. In contrast, recording local field potential (LFP) activity is considerably less complex from a methodological point of view. Given that LFP activity is thought to reflect the pattern of incoming synaptic information at a given recording site, it may also contain task-critical information that could be decoded with the proper analytical tool. Here we test this hypothesis using recordings of LFP activity across the proximo-distal axis of CA1 as rats performed non-spatial and spatial behaviors (an odor sequence memory task and navigating a linear track, respectively). We developed a novel LFP decoding framework utilizing deep learning which is able to sequentially integrate information of various orders, extract knowledge from high-order neighbors, and provide meaningful and interpretable results by identifying influential electrodes. In particular, our method consists of two components: an estimation model using a latent representation of the activity to decode the content of individual trials, and an interpretation model that identifies patterns in the activity across electrodes that significantly predict trial-specific information. Using LFP activity alone, we found that the model can accurately identify trial type for both non-spatial and spatial information as well as the informative electrodes distributed across the CA1 axis. Notably, the observed gradient on informative electrodes for non-spatial and spatial information was consistent with known anatomical inputs. Post-hoc analysis indicates that the primary difference in the LFP power between informative and uninformative electrodes was in the beta range (20-40 Hz). These findings suggest that CA1 LFP activity contains sufficient information to decode trial-specific content and may complement spiking signals by reflecting task-critical information from upstream structures.

Disclosures: K.W. Cooper: None. **B. Shahbaba:** None. **N.J. Fortin:** None.

Poster

PSTR368: Oscillations Underlying Memory Functions

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Program #/Poster #: PSTR368.05/V20

Topic: H.08. Learning and Memory

Title: Ca3 neuronal dynamics during sequence memory

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Abstract: Theory proposes that area CA3 of the hippocampus supports sequence generation via recurrent circuitry. Along these lines, silencing of CA3 inputs to CA1 results in disruptions of theta sequences and aberrant spatial coding. Little is understood, however about the involvement of CA3 in learning new sequences or in long-term memory of well-known sequences, as previous work has focused on working memory. Here we present a novel spatial reward sequence task suitable for longitudinal recordings from CA3 with high density silicone probes. Mice learn to sequentially visit reward locations in an octagonal maze equipped with 8 ports (A:H) for reward delivery (5% sucrose). First, mice are trained to learn a sequence of 3 ports (A-E-C). After mice are well trained, (2 consecutive days above 70% of trials of fully correct sequences) mice are trained on a new different sequence (F-B-D). Mice (n=6, 3m, 3 f) learned both sequences within 7 days, suggesting that the learning rule is not transferred between sequences. Current analyses are underway to determine CA3 single unit and oscillatory activity during learning and after mice are well trained.

Disclosures: N. Masala: None. **G. Tarcsay:** None. **L.A. Ewell:** None.

Poster

PSTR368: Oscillations Underlying Memory Functions

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Topic: H.08. Learning and Memory

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University of Washington

Title: Neural oscillatory dynamics of the dorsal hippocampus during a complex strategy switching task

Authors: *M. BOTTOMS, J. T. MILES, S. J. Y. MIZUMORI;
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Abstract: Previous work has shown frequency-specific modulation of dHPC neural activity during simple behavioral tasks, suggesting that there are shifting neural population dynamics during different task phases and animal behaviors. Relatively little is known about task-relevant orchestrated shifts in theta, beta, and gamma oscillations when rats perform a complex task that requires repeatedly adapting behavioral strategies based on changing reward contingencies. To address this gap in knowledge, we used a spatial set-shifting task developed by Miles et al., 2024 (in press) to determine whether dHPC plays a specific role in strategy switching. The task

requires rats to use two spatial strategies on an elevated plus maze: 1) alternating between east and west reward locations or 2) always going to the same reward location (e.g. only east or only west). Each session contains three uncued changes to the correct strategy, the transitions between which are called block switches. This requires the animal to recognize and adapt to changes in reward contingencies. Using recency-weighted Bayesian inference, we quantify how flexibly a subject is behaving, as well as the estimated trial where a subject has learned the correct strategy within a given strategy block (referred to as the learning point). By recording field potentials while rats are performing the task, we correlate their behavior with the neural activity of dHPC. At the single trial level, we show that theta and beta power peaks when the rat is expecting a reward. On trials after an animal has reached the learning point, theta and beta power increases. Gamma power decreases when rats are behaving more flexibly. dHPC, therefore, appears to track task demands, with the strength of each oscillatory frequency seeming to differentially correlate with specific behaviors or task dynamics. Our finding is consistent with the hypothesis that dHPC responds to contextual changes by entering into a neural state that supports heightened attention to help update the rat's strategy.

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Poster

PSTR368: Oscillations Underlying Memory Functions

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Program #/Poster #: PSTR368.07/V22

Topic: B.07. Network Interactions

Support: NIH R01NS054281

Title: Theoretical and computational analysis of synchronization and frequency control of theta nested gamma in the medial entorhinal cortex

Authors: *A. VEDURURU SRINIVAS[1], B. D. WILLIAMS[2], R. BARAVALLE[3], J. A. WHITE[2], C. C. CANAVIER[1];
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Abstract: Optogenetic stimulation of the medial entorhinal cortex (mEC) in mouse slices at theta frequencies elicits nested fast gamma at ~150 Hz oscillations when driving PV+ inhibitory neurons only, resulting in inhibitory network gamma (ING). When ChR2 is expressed primarily in excitatory stellate and pyramidal cells under the CaMKII promotor or in both stellate and inhibitory cells under the Thy1 promotor, the frequency of nested fast gamma drops to ~100 Hz (Williams et al poster) in pyramidal-interneuronal network gamma (PING). Previous work (Brunel and Wang 2003) assumed a stochastic population oscillator in which all neurons were fluctuation driven. They showed that for ING the frequency in LIF networks is determined largely by the inhibitory phase lag whereas in PING the population frequency at the bifurcation

is now determined by the sum of excitatory and inhibitory synaptic phase lags. However, the interneurons under optogenetic theta drive are clearly mean driven and do not require excitatory input to fire, so this mechanism likely does not apply here. A second mechanism they proposed by which adding pyramidal-to-pyramidal connections to a network with all other types of connections tends to decrease network frequency because these connections tend to prolong the positive phases of each cycle of the oscillation. Since there is no recurrent connectivity between stellate cells this mechanism is also not likely. Our simulations of these ING and PING networks of the mEC suggested two mechanisms by which adding stellate cells to the ING network can slow the frequency. The first is that the stellate cells set the frequency of the network by grouping the firing of the interneurons into bursts; there is some evidence for this mechanism in Pastoll et al 2013. The second mechanism is simply that the excitation recruits more inhibitory neurons into the oscillation and also synchronizes them much more strongly. In the PV-Cre and Thy1-Cre mice, the interneurons are directly excited by the optogenetic stimulation and thus do not require synaptic excitation to fire, the classic PING mechanism proposed by Kopell and Borgers and colleagues does not apply. We apply phase response theory to show how reciprocal coupling to a cluster of sparsely firing stellate cells can synchronize mean-driven interneuronal populations that cannot synchronize themselves. Phase response theory suggests that level of synchronization in the network can be controlled by the reversal potential of $GABA_A$ synapses. We also present a mean-field theory method for coupled oscillators based on the phase response curve.

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Poster

PSTR368: Oscillations Underlying Memory Functions

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Topic: B.07. Network Interactions

Support: NIH F31NS134309
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Title: Ex vivo voltage imaging reveals mechanisms of theta-nested gamma oscillations in the medial entorhinal cortex

Authors: *B. D. WILLIAMS[1], S. XIAO[1], C. C. CANAVIER[2], X. HAN[1], J. A. WHITE[1]; [1]Biomed. Engin., Boston Univ., Boston, MA; [2]Cell Biol. and Anat., LSU Hlth. Sci. Ctr. New Orleans: Louisiana State Univ. Hlth. Sci. Ctr., New Orleans, LA

Abstract: The medial entorhinal cortex (MEC) performs critical functions in spatial navigation, learning, and memory. Many neurons in layer 2/3 of the MEC fire at periodic locations which generate a grid-like (‘grid cells’) firing pattern when traversing an open field. A network-wide

theta (4-12 Hz) frequency oscillation modulates the firing rates of these grid cells. Additionally, higher frequency gamma (40-140 Hz) oscillations are nested within the network theta oscillation and are hypothesized to increase the synchrony of grid cell firing (Reifenstein et al. 2012 PNAS 109:6301-6306). In the pyramidal-interneuron network gamma (PING) model, pyramidal cells excite local interneurons which provide inhibitory feedback. The timescale of the feedback loop generates oscillations in the gamma frequency range. Recent advances in fluorescent voltage indicators have enabled the imaging of tens to hundreds of neurons simultaneously. To investigate the mechanisms of theta-nested gamma oscillations, we non-specifically expressed the chemigenetic voltage indicator, Voltron2, in layer 2/3 MEC of transgenic CaMKIIα-ChR2 mice. Acute brain slices were incubated in JF585 dye and imaged by a targeted-illumination confocal microscope during theta-frequency optogenetic stimulation of local excitatory neurons. The local field potential (LFP) was simultaneously recorded to capture theta-nested gamma oscillations in the network during a PING mechanism. A range of theta frequencies were used for stimulation: 4, 8 and 12 Hz. Parvalbumin (PV) interneurons were identified post-hoc using immunohistochemistry. Using these techniques, we have recorded the activity of 60+ neurons in a single field of view and over 400 neurons across 6 mice. We find that the gamma frequency of the LFP oscillations does not change when stimulating with different theta frequencies. However, the peak gamma power occurred earlier in the theta phase at 4 Hz compared to 8 and 12 Hz. Preliminary results also show that excitatory cells alternate to fire on different gamma cycles, as expected, due to their low firing rates. Further analysis will reveal the spatial extent of excitatory and inhibitory cell firing during the generation of theta-nested gamma oscillations via a PING mechanism. These results will provide mechanistic insight into how excitatory and inhibitory neurons in layer 2/3 mEC organize during theta-nested gamma oscillations as observed during spatial navigation.

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Poster

PSTR368: Oscillations Underlying Memory Functions

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Topic: H.08. Learning and Memory

Support: NIH Medical Research Scholars Program
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Title: Hippocampal Micro-stimulation Modulates High-Frequency Ripple Oscillations in Humans

Authors: *D. A. ZARRIN[1,2], U. R. MOHAN[3], O. E. FRUCHET[4], K. K. SUNDBY[1], J. I. CHAPETON[7], W. XIE[5], S. INATI[6], K. A. ZAGHLOUL[8];
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UCLA, Los Angeles, CA; [3]NINDS, NIH, Washington, DC; [4]Neurosurg., NIH, Bethesda, MD; [5]Dept. of Psychology, NIH, College Park, MD; [6]NINDS, NIH, Bethesda, MD; [7]NINDS, NIH, Natl. Inst. of Neurolog. Disorders & Stroke (NINDS), Bethesda, DC; [8]NINDS, Bethesda, MD

Abstract: High-frequency oscillation events, known as ripples, have been shown to underly human memory encoding and retrieval. Numerous studies have demonstrated an increase in coupled ripples between the medial temporal lobe and association cortices during successful memory retrieval in awake humans. However, studies have yet to utilize brain stimulation to causally explore the role of ripples in human memory. While rodent studies have shown preliminary evidence that hippocampal stimulation holds the potential to disrupt or elongate ongoing ripples and even induce new ripples, we do not yet understand how stimulation modulates ripples in humans. To explore the feasibility of inducing ripples via open-loop hippocampal micro-stimulation in humans, we collected human intracranial EEG recordings from neurosurgical epilepsy patients while delivering open-loop stimulation to the hippocampus at a range of microampere-level amplitudes. We delivered stimulation at 9 distinct hippocampal locations in 2 patients. On each qualifying electrode, we conducted a 5-minute stimulation sequence consisting of five cycles of a 30-second period without stimulation followed by a 30-second stimulation train with either 1 or 5 biphasic pulses (at 100 Hz) delivered once per second. We increased amplitudes on each successive stimulation train and found a significant elevation in ripple rate during stimulation trains compared to no-stimulation baselines, which increased with stimulation amplitude both within and across patients. Further, our data demonstrates alterations in cortical ripple rates coinciding with stimulation on select hippocampal electrodes. In such instances, the degree of ripple coupling between cortical sites and the stimulated hippocampal locations prior to stimulation correlated with the magnitude of cortical ripple rate increase in response to stimulation. We provide direct evidence in humans that hippocampal stimulation locally amplifies high-frequency ripple oscillations. Further, we provide the first causal evidence probing the mechanisms of ripple-mediated dialogue between the hippocampus and association cortex.

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Poster

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Program #/Poster #: PSTR368.10/V25

Topic: H.08. Learning and Memory

Support: NIH/NINDS R01 NS-021135
NIH/NIMH R01 MH-120194
NSF DRL2201843

Title: Human hippocampal-frontal theta dynamics during complex rule learning

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Abstract: Subjects (n=18) undergoing intracranial monitoring were implanted with stereo-EEG electrodes across the medial temporal and frontal lobes and completed an experiment in which they learned, through trial-and-error, to classify stimuli using increasingly complex rules that ranged from the identification of individual features (e.g. "blue") to the integration and negation of multiple features (e.g. "blue and not square"). We parameterized the power spectrum of each electrode during the feedback period into an aperiodic (1/f) component and a periodic component consisting of oscillatory peaks, identifying a prominent cluster of theta-band (3-8 Hz) peaks in the overall distribution (mean center frequency: 6.65 Hz, std: 1.56). For electrodes with a theta peak in the hippocampus (n=67) or in lateral (n=175), orbital (n=48), or medial (n=55) frontal areas, we computed the extent of theta-gamma phase-amplitude coupling (PAC) during the feedback period and identified a bout of PAC in hippocampal electrodes emerging ~ 400 ms after the onset of feedback, which was relatively greater in correct rather than incorrect trials ($p < 0.05$). Next, we selected subjects with both hippocampal and frontal electrodes that had theta peaks (n=11 subjects, 422 total pairs) and computed the phase-locking value (PLV) for the theta range within these pairs. We found a substantial increase in PLV beginning with the onset of feedback and peaking in magnitude at ~ 500 ms after feedback, which was relatively greater in correct rather than incorrect trials ($p < 0.001$). Taken together, these analyses implicate hippocampal theta-gamma PAC and frontal-hippocampal theta synchronization as putative mechanisms for feedback-driven rule updating and support cognitive theories of rule-based concept learning that privilege updating in response to positive feedback.

Disclosures: M.A. Gorenstein: None. **P. Brunner:** None. **J.T. Willie:** None. **M. Dastjerdi:** None. **J.J. Lin:** None. **R.T. Knight:** None. **S.T. Piantadosi:** None.

Poster

PSTR368: Oscillations Underlying Memory Functions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.11/V26

Topic: H.08. Learning and Memory

Support: NIH T32 NS047987

Title: Temporal dynamics of EEG oscillation as measured by spectral power volatility: rest-task stability and cognitive relevance

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Abstract: The temporal dynamics of neural oscillations play a crucial role in human cognition. Previous studies have used temporal volatility as a metric to gauge moment-to-moment fluctuation in EEG spectral power involving verbal puzzles such as anagrams and compound remote associate problems (CRA). Spectral power volatility has been associated with trial outcomes with lower volatility predicting better performance in terms of solving success and solving time (Yu et al., 2024). To further investigate spectral power volatility as a reliable index for cognition, this study examined resting-state EEG data from the same group of participants (N=40) who engaged in anagrams and CRAs in separate task sessions. Spectral power volatility was computed across a range of frequencies from 4 Hz to 50 Hz at each electrode. Results indicated that volatility was generally higher during rests compared to the task sessions. Importantly, individual volatility was correlated across rest and task sessions (rest and anagram r = .42, p = .008, rest and CRA r = .43, p = .008), supporting spectral power volatility as a stable trait for characterizing oscillation dynamics. Furthermore, consistent with findings from previous research, volatility during eyes-closed rest periods was negatively correlated with the percentage of problems solved in both anagrams (r = -.31, p = .048) and CRAs (r = -.33, p =.038). In sum, spectral power volatility varies systematically between rest and task conditions while exhibiting within-subject stability. Low volatility, indicative of less rapid transitions between neural oscillatory synchronization and desynchronization, is associated with better problem-solving performance at both within-subject and between-subject levels. Thus, volatility can complement existing measures and offer valuable insights into cognition-related oscillation dynamics.
References: Yu, Y., Oh, Y., Kounios, J., Beeman, M., Electroencephalography Spectral-power Volatility Predicts Problem-solving Outcomes. J Cogn Neurosci 2024; 36 (5): 901-915. doi: https://doi.org/10.1162/jocn_a_02136

Disclosures: Y. Yu: None. **Y. Oh:** None. **J. Kounios:** None. **M. Beeman:** None.

Poster

PSTR368: Oscillations Underlying Memory Functions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.12/V27

Topic: H.08. Learning and Memory

Support: R00NS115918
R01MH107512
R01NS021135

Title: Differential medial temporal-prefrontal connectivity determined by stimulus onset or HFB peak network timing

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Abstract: The medial temporal lobe and prefrontal cortex coordinate their activity in the service of memory. Some of this coordination is driven by external stimulation (e.g. processing an image), but some is driven by internal processing (e.g. recruitment of one area by activity in another). Prior literature has focused on analyzing data temporally aligned to external events, but this may leave undetected aspects of mnemonic processing organized around internal events. We used intracranial recordings from 36 neurosurgical patients (22 male, 19 ± 4.7 years old) to investigate connectivity between these regions during encoding and recognition testing of natural scene images. From an initial set of 605 channels, we selected only those with task-related high frequency broadband (HFB; 70-150 Hz) responses--which index neuronal population activity--yielding 181 dorsolateral prefrontal cortex (dlPFC), 30 anterior cingulate cortex (ACC), 30 polar prefrontal cortex (pPFC), 67 parahippocampal and rhinal cortex (PHRC), and 29 hippocampal (HC) channels. Intersite phase clustering (ISPC) was used to assess inter-channel pairwise connectivity between 2 and 25 Hz. ISPC was calculated on data aligned in time in two ways: to the onset of the image and to the peak of HFB activity in each trial. Cluster-corrected linear mixed-effects models assessed differences in connectivity between hit and miss trials at every time-frequency point. Both methods of temporal alignment yielded connections that were greater for successful versus failed memory encoding and retrieval. However, the patterns of significant connections were different. When time was aligned to image onset, none of the ACC's connections with other regions were modulated by memory during either encoding or retrieval. By contrast, when time was aligned to HFB peak, the ACC's connections with the PHRC (2-4.5 Hz) and pPFC (4.5-8 Hz) were increased for successful over failed encoding, and the ACC's connections with the HC and dlPFC (both 2-4.5 Hz) were increased for successful over failed retrieval. Other mnemonic connections were more apparent in the image-aligned analysis. The dlPFC exhibited greater connectivity with the HC (2-4.5 Hz) during successful encoding compared to failed encoding, a difference that was absent when time was aligned to HFB peak. Graph theoretic analysis revealed that whole-brain networks were less connected during successful encoding at the times and frequencies when connections between our regions of interest were increased for successful encoding, an effect that may serve to heighten contrast in the network.

Disclosures: A.J.O. Dede: None. **Z.R. Cross:** None. **S. Gray:** None. **Q. Yin:** None. **P. Vahidi:** None. **E. Asano:** None. **S. Schuele:** None. **J. Rosenow:** None. **J. Wu:** None. **J. Raskin:** None. **J. Lin:** None. **A. Shaikhouni:** None. **P. Brunner:** None. **J.L. Roland:** None. **I. Saez:** None. **F. Girgis:** None. **R.T. Knight:** None. **N. Ofen:** None. **E. Johnson:** None.

Poster

PSTR368: Oscillations Underlying Memory Functions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.13/V28

Topic: H.08. Learning and Memory

Support: R00NS115918
R01MH107512
T32MH067564
NSF2234667
R01NS021135
R01NS021135

Title: Distinct slow and fast theta signatures of memory formation within the developing medial temporal lobe in humans

Authors: *Y. RIVERA[1], S. GRAY[1], A. DEDE[2], Q. YIN[3], P. VAHIDI[4], W. CHANG[5], E. M. RAU[6], S. SCHUELE[7], J. ROSENOW[7], J. WU[8], J. RASKIN[8], A. SHAIKHOUNI[9], K. AUGUSTE[10], E. F. CHANG[11], P. BRUNNER[12], J. L. ROLAND[13], R. T. KNIGHT[14], E. ASANO[15], N. OFEN[16], E. JOHNSON[1];
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Abstract: The medial temporal lobe (MTL), composed of the hippocampus (HC) and parahippocampal gyrus (parahippocampal and rhinal cortices; PHG), is crucial to episodic memory and posited to support memory formation in children. The neurophysiological mechanisms by which different MTL regions support ongoing memory development and relate to individual factors remains unknown. We examined theta signatures of memory formation in the HC and PHG of individuals aged 5-28 years and related them to HC volume and age. We capitalized on a rare opportunity to record intracranial EEG data from 41 neurosurgical patients (19F, 22M; 167 MTL electrodes) while they studied visual scenes, and indicated whether each scene was indoor/outdoor, in preparation for a memory recognition test. We observed a positive age by recognition accuracy effect and no relationship between age and HC volume, both consistent with healthy populations. After separating oscillatory components from aperiodic 1/f activity, we identified distinct slow (~2-4 Hz) and fast theta (~4-8 Hz) oscillations per electrode. We first examined variability in slow and fast theta frequencies. Slow theta frequencies were

explained by the interaction of MTL region and HC volume, such that HC slow theta frequencies increase with HC volume while PHG frequencies decrease. Fast theta frequencies were explained by the interaction of MTL region and age, such that HC fast theta frequencies decrease with age while PHG frequencies increase. We then identified slow and fast theta power and phase resetting signatures of memory formation by comparing subsequently remembered (hit) and forgotten (miss) scenes using cluster-corrected linear mixed-effects models. Successful memory was associated with 1) a positive main effect (hit > miss) in slow theta phase resetting across MTL regions at and immediately following scene onset and 2) a negative main effect (hit < miss) in fast theta power after the indoor/outdoor response. Additionally, we observed regional main effects in power such that there was greater slow and fast power in HC relative to PHG between image onset and response time. Our results establish distinct mechanisms by which slow and fast theta oscillations support memory formation in the developing human brain.

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Poster

PSTR368: Oscillations Underlying Memory Functions

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR368.14/V29

Topic: H.08. Learning and Memory

Support: R00NS115918
R01MH107512
R01NS021135
T32NS047987

Title: Intracranial EEG signatures of successful memory in a default mode subnetwork during human brain development

Authors: *J. P. KELLY[1], A. J. O. DEDE[1], S. GRAY[1], Q. YIN[2], P. VAHIDI[3], E. ASANO[4], J. WU[5], J. RASKIN[5], S. SCHUELE[1], J. ROSENOW[1], A. SHAIKHOUNI[6], P. BRUNNER[7], J. L. ROLAND[8], K. AUGUSTE[9], R. T. KNIGHT[10], N. OFEN[3], E. JOHNSON[11];
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Abstract: Posterior cingulate cortex (PCC), the precuneus (PRC), and the angular gyrus (ANG) are major parietal nodes of a default-mode subnetwork supporting episodic memory. Previous intracranial EEG (iEEG) studies of these parietal regions suggest that successful encoding and retrieval is associated with increased high-frequency broadband activity (HFA, 70-150 Hz) and decreased theta-alpha activity (2-12 Hz) >300 ms after stimulus onset. It is unknown whether these same dynamics support memory in parietal regions of children and adolescents, and whether age-related variability in these functional dynamics corresponds with age-related variability in memory performance or brain structure, as measured by cortical thickness in the same regions. Here, we analyzed iEEG data recorded from 25 neurosurgical epilepsy patients aged 5-30 years (11 females) performing an old/new scene recognition task. Trial-by-trial iEEG data from the study (encoding) and test (retrieval) phases of the task were analyzed as a function of retrieval success (remembered "hit" trials vs. forgotten "miss" trials). After first identifying task-positive electrodes in all regions, we found that in PCC, both successful encoding and retrieval were associated with increases in HFA >500 ms after image presentation. Successful encoding was also associated with a pre-stimulus increase in theta-alpha activity. Conversely, in PRC, increased HFA >500 ms after image presentation was associated with failed retrieval. In ANG, successful memory was associated with increased activity across low-frequeny bands at encoding (<1300 ms, 2-34 Hz), which flipped to decreased activity at retrieval (500-1000 ms, 4-34 Hz). Together, these results identify HFA signatures of successful memory in adolescents similar to those found in adults, while also identifying novel low-frequency signatures of successful memory pre- and post-stimulus. Data collection is ongoing. Further analysis will test whether these memory effects increase with age and correspond with age-related cortical thinning of these regions.

Disclosures: J.P. Kelly: None. **A.J.O. Dede:** None. **S. Gray:** None. **Q. Yin:** None. **P. Vahidi:** None. **E. Asano:** None. **J. Wu:** None. **J. Raskin:** None. **S. Schuele:** None. **J. Rosenow:** None. **A. Shaikhouni:** None. **P. Brunner:** None. **J.L. Roland:** None. **K. Auguste:** None. **R.T. Knight:** None. **N. Ofen:** None. **E. Johnson:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.01/V30

Topic: H.08. Learning and Memory

Support: R01GM128183

Title: Intranasal Insulin Mitigates Memory Impairment and Microglial Activation in Pseudo-Aged Mice with Genetic Ablation of Dentate Hilar Somatostatin-Positive GABAergic Interneurons

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Abstract: Aging is a complex process that frequently includes cognitive decline with memory loss, presenting significant challenges for the elderly. In the hippocampus, vital for cognition, learning, and memory, the number of somatostatin-positive (Sst+) GABAergic interneurons in the hilar region of the dentate gyrus decreases with age, resulting in age-related memory impairment. We previously showed that selective ablation of Sst+ dentate hilar interneurons is sufficient to induce cognitive dysfunction, resulting in an animal model of hippocampal aging (pseudo-aged mice). Additionally, brain insulin and insulin receptor expression decline with age. Intranasal insulin (INS) has shown promise in improving learning and memory in Alzheimer's disease. In this study, we investigated the effects of INS in pseudo-aged mice with genetically ablated dentate hilar Sst+ interneurons, which were generated by bilateral injection of AAV5-EF1α-mCherry-flex-dtA into the dentate hilus of Sst-IRES-Cre mice aged 3-4 months. Following a 3-week recovery period post-injection, INS was administered daily for 9 days. Subsequently, learning and memory functions were assessed, along with molecular studies. Our findings indicate that INS treatment ameliorates working memory deficits in the Y maze test, recognition memory deficits in the novel object recognition test, and non-declarative associative memory deficits in the trace fear conditioning test in the pseudo-aged mice compared to control mice. Furthermore, INS treatment attenuated microglial activation and increased BDNF expression in the pseudo-aged mice. INS holds promise for alleviating memory impairment and reducing microglial activation in this model of hippocampal aging, providing a potential therapeutic avenue for addressing age-related cognitive decline. Further research is needed to elucidate the precise mechanisms underlying these effects and to evaluate the translational potential of INS in clinical settings.

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Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.02/V31

Topic: H.08. Learning and Memory

Title: Rapamycin, A Calorie Restriction Mimetic for the Treatment of Alzheimer’s Disease: A Preclinical Investigation

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Abstract: Laboratory experiments have repeatedly demonstrated that organisms can live longer and healthier by reducing their calorie intake. With the implication that the same might be true for humans, calorie restriction mimetics have generated lot of interest in the treatment of age related disorders. Rapamycin, also known as sirolimus, is an immunosuppressant drug that was approved by the Food and Drug Administration (FDA) in 1999. The therapeutic drug rapamycin, which is normally used in cancer therapy and after organ transplants, can extend the lifespan and health span of laboratory animals. Understanding the target of rapamycin (TOR) signaling pathway in model organisms like yeast, worms, and flies provides valuable insights into potential interventions for age-related disorders in humans. In the current research work, rapamycin was evaluated in an animal model of Alzheimer's disease (AD) as treatment approach for age related disorders. Rats received intracerebroventricular (ICV) infusion of amyloid beta (1-40) for 14 days through osmotic pumps and were treated with rapamycin (1 or 3 mg/kg, *p.o*.) simultaneous to the infusion. Control group of rats received ICV infusion of saline or amyloid beta (1-40) alone. Animals were subjected to evaluation in radial arm maze followed by assessments of biomarkers related to oxidative stress (Malondialdehyde, glutathione), aging (mammalian target of rapamycin [mTOR], SIRT-1), cognition (BDNF) and amyloid beta levels. Impaired cognitive abilities were observed in rats with amyloid beta (1-40) infusion; however rapamycin produced significant decrease in total errors and increased % choice accuracy. Similarly, oxidative stress evaluated through the measurement of malondialdehyde was increased in animals treated with amyloid beta (1-40) alone, and rapamycin produced a decrease in levels of oxidative stress marker and decreased expression of mTOR. Increased expression of SIRT1 and BDNF levels were also observed with simultaneous treatment of rapamycin and amyloid beta (1-40) infusion. Non-significant changes were observed in the feed intake and body weight either with the infusion alone, rapamycin treatment alone, or with simultaneous treatment of rapamycin to infusion. Results from the current studies indicate that calorie restriction mimetics might have potential beneficial effects in the management of AD through the improvement of anti-aging properties.

Disclosures: V. Benade: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Krishnadas:** None. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.03/V32

Topic: H.08. Learning and Memory

Title: Effect of astaxanthin supplementation on cognitive, mood, functionality and quality of life of college football players

Authors: M. SAMUDIO-CRUZ[1], G. LARA HERNÁNDEZ[2], J. ANDRADE-CABRERA[3], H. AVILÉS-ARNAUT[4], E. PÉREZ SOTO[5], ***L. SANCHEZ-CHAPUL**[6];
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Abstract: Effect of astaxanthin supplementation on cognitive, mood, functionality and quality of life of college football players
Astaxanthin (ASX) is a lipid-soluble carotenoid found in seafood that is gaining attention in scientific literature, because of its benefits in muscle recovery, fatigue, aging, and cognition. In exercising humans or high-performance athletes (i.e football players), these observations have yet to be consistently realized. Football is a highly competitive sport that demands peak cognitive performance from players, thus understanding how ASX supplementation may enhance cognitive function to optimize players' performance, could have broader implications for public health and other sports with similar cognitive demands. This study aimed to investigate the effect of astaxanthin supplementation on cognitive, mood, functionality and quality of life of Mexican football players. A total of 68 college football players with mean age of 21.26 years (SD=4.12) were included. Athletes were supplemented with an ASX nutritional supplement (50mg/ml, 5 days a week) during 6 months. The cognitive, mood, functional status and quality of life were evaluated before and after 6 months of supplementation, using the Montreal Cognitive Assessment, the Beck Depression and Anxiety Inventories, Bayer Activity of Daily Living Scale and World Health Organization Quality of Life BREF. The differences between the variables pre and post intervention were assessed using the Wilcoxon test. Statistical significance was set at $p<0.05$. No statistically significant differences were observed in the cognitive state ($p=0.101$); but after ASX supplementation, we found significant differences in memory, specifically in spontaneous evocation ($p=0.005$) with keys ($p=0.020$) and recognition ($p=0.034$), as well as a significant increase in quality of life ($p=0.005$). The rest of the cognitive processes did not show differences pre and post supplementation. Although there were no significant differences in mood, functionality showed a trend towards difference, with greater functional independence observed. The ASX supplementation is associated with an improvement in learning and memory capacity, specifically in the processes of retrieval and storage of information, which has been reported in both, healthy subjects and in Alzheimer's disease. The increase in quality of life could be attributed to both, a better cognitive performance as well as the effects of the ASX supplement *per se*.

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Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.04/V33

Topic: H.08. Learning and Memory

Support: Dr. Hunsberger's RFU lab start-up package

Title: Alprazolam impairs fear memory and alters dorsoventral CA1 neuronal ensembles in female mice

Authors: *K. KAPLAN[1], L. TOENNIES[1], H. C. HUNSBERGER[2];
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Abstract: Benzodiazepines (BZDs) are commonly prescribed anxiolytic drugs that act on GABAa receptors and can result in anterograde amnesia, or the inability to form new memories. While BZDs have been used for over 60 years, the brain regions and neuronal mechanisms responsible for this detrimental side effect are largely unknown. Continued use of BZDs may potentially lead to memory impairment and cognitive decline later in life. To analyze the effects of BZDs on long-term memory, ArcCreER^{T2} x eYFP mice were injected with Alprazolam 30 minutes prior to a 3-shock contextual fear conditioning (CFC) procedure. This ArcCreER^{T2} x eYFP mouse model allows us to tag neuronal ensembles active during a learning or encoding experience by using Arc as an immediate early gene (IEG) promotor. We then re-exposed mice to the same context 5 days later and analyzed retrieval cell activation using a second IEG, cFos. This allows us to determine which brain regions undergo changes after BZD injection and how cellular changes relate to freezing behavior (a proxy for memory). Additionally, we address the questions of whether BZDs induce state-dependent memory or alter initial consolidation by altering the timelines of injection to circumvent the sedative properties of BZDs. We found that 1) BZD-treated female mice exhibit a decrease in memory retention, 2) BZD-treated female and male mice show a decrease in memory retention with saline injection prior to re-exposure, and 3) BZD injection immediately after CFC training enhances memory in male mice. Cell counts show that BZD-treated female mice exhibit increased EYFP+ (encoding) activation in the dCA1. An opposite pattern was observed in the vCA1 where BZD-treated females showed less cFos+ activation, suggesting that ventral hippocampal activity is dampened with BZD injection, but the dorsal hippocampus is still encoding information. We are further analyzing cell counts in other hippocampal and amygdala regions. This project will help us understand the long-term memory deficits associated with BZD use. As the ArcCreER^{T2} mouse allows for brain-wide neuronal tagging, we can potentially discover novel brain regions involved in these side effects. Future studies will examine the impact of chronic BZD use on aging and Alzheimer's disease.

Disclosures: K. Kaplan: None. **L. Toennies:** None. **H.C. Hunsberger:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.05/V34

Topic: H.08. Learning and Memory

Title: Impact of serotonin 6 receptor activation on consolidation of spatial learning

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Abstract: Recent studies have highlighted the 5-HT6 receptor as a novel target for cognitive enhancement. However, the majority of the research investigates the effects of 5-HT6 receptor blockade on executive functioning, leaving many unanswered questions on how 5-HT6 activation affects cognition. The current study aims to address these gaps within the literature by examining the effects of the 5-HT6 agonist EMD 386088 on the consolidation of learning. Specifically, we aim to examine how 5-HT6 receptor agonism impacts the consolidation of a probabilistic spatial discrimination task. To do so, male and female C57BL/6J mice were tested in a spatial probabilistic learning paradigm, and received systemic injections of either 0, 1, or 5 mg/kg EMD386088 treatment immediately after task training, 24 hours before retention testing, to target distinct consolidation phases of learning. During the retention test, both doses of 1 mg/kg and 5 mg/kg significantly impaired the performance of male and female mice. Although there were no significant differences between the two doses, mice treated with EMD386088 required significantly more trials to reach retention criterion compared to vehicle-treated mice. Female mice treated with 1 mg/kg EMD386088 made significantly more regressive errors showing a significant impairment in their ability to maintain a new choice pattern after shifting to the correct choice. The current findings demonstrate the potential sensitivity of treatment timing in the application of novel therapeutics aimed at stimulating 5-HT6 receptors and their impact on cognitive outcomes.

Disclosures: D. Amodeo: None. **C. cavazos:** None. **J. Robinson:** None. **M.R. Gonzales:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.06/V35

Topic: H.08. Learning and Memory

Support: CONAHCyT CF-2023-G-597
CONAHCyT 821695

Title: Chronic administration of cb2 receptor agonist does not produce changes in spatial learning<memory but it reduces weight gain

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Abstract: Obesity is a complex chronic disease in which fat deposits increase excessively < is associated with the development of metabolic alterations that elevate the risk of type 2 diabetes mellitus < cardiac pathologies, also lead to damage to the CNS. One of the models widely used in the study of obesity is the Zucker rat, which develops hyperphagia < obesity from an early age as well as CNS alterations associated with neuroinflammation < cognitive impairment. Due to the alarming worldwide prevalence of obesity new therapeutic strategies are being sought < one of the most promising targets focuses on the pharmacological modulation of the CB2 receptor through specific agonists. Such as JWH-133, a synthetic cannabinoid that has been shown to reduce food intake < induce thermogenesis in adipose tissue, as well as to improve spatial memory. Therefore, the aim of the present study was to analyse the role of chronic CB2 receptor stimulation on the metabolic profile < spatial memory in obese Zucker rats. Sixteen LZDF (Lean Zucker Diabetic Fatty) < 16 OZDF (Obese Zucker Diabetic Fatty) rats were used, at 12 weeks of age the animals were divided into the following groups: LZDF+VEH (n=8), OZDF+VEH (n=8), LZDF+JWH-133 (n=8) < OZDF+JWH-133 (n=8) < started the administration of 0.2mg/kg JWH-133 30 minutes prior of the glucose tolerance test. Over the next 5 days, we assessed learning in the Morris water maze, 14 days later we assessed memory < the next day the animals were euthanised until daily administration of JWH-133 was maintained; blood samples were collected for metabolic profile analysis. The results show that administration of 0.2 mg/kg JWH-133 reduces weight gain in OZDF rats. Moreover, it was found that at 12 weeks of age OZDF rats do not show deficits in spatial learning < memory < that JWH-133 has no effect on learning or memory, as no significant differences were found in escape latency, latency to first crossing to the platform area or in the number of entries to the same area. In the other hand, administration of JWH-133 was not effective in reducing glucose, triglycerides, < cholesterol levels. Given the above, we can conclude that JWH-133 is effective in controlling body weight without adverse effects on spatial learning < memory.

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Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

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Program #/Poster #: PSTR369.07/V36

Topic: H.08. Learning and Memory

Support: NSFC31872311
NSFC82104415
Provincial SFC212300410027

Title: Isoquercitrin-ligustrazine Co-polymorph Regulates Microgliosis Mediated Neuronal Activity in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is one of the most common neurodegenerative disorders characterized by memory loss and cognitive impairments. In typical AD cases, microglia activation occurs in various brain regions and plays a pivotal role in AD pathology. Since the connection between microgliosis and AD development is not fully elucidated, pharmacological interventions on microglia-neuronal regulation remain underexplored. Isoquercitrin and ligustrazine are noted for their anti-inflammatory, antioxidant, and metabolic regulatory effects. Here, we aim to show how isoquercitrin-ligustrazine co-polymorph (ILCP) affects microgliosis, thereby regulating neuronal activity in AD. An AD mouse model has been established through ventricular injection of $A\beta_{1-42}$, and cognitive functions as well as pathological markers have been assessed across the development of AD symptoms. Microglial phenotypes, activation, and impacts on neuronal activity in multiple brain regions have been investigated. Our findings indicate that ILCP effectively facilitates the phenotypic transition of microglia between M1 and M2 and affects neuronal activities. ILCP application also reduces β-amyloid plaque deposition in cortical and hippocampal regions and diminishes neuronal injury and apoptosis. These changes correlate with the amelioration of cognitive impairments and are linked to the suppression of neuroinflammation. Overall, our results addressed the effects of ILCP on regulating microgliosis and protective effects in cognitive functions, highlighting a therapeutic potential in the development of AD.

Disclosures: Y. Yang: None. **X. Long:** None. **J. Shi:** None. **Y. Xie:** None. **X. Xie:** None. **X. Pang:** None. **L. Du:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.08/V37

Topic: H.08. Learning and Memory

Title: Neuropharmacological Exploration: Novel chalcone based small molecules ameliorate STZ induced memory dysfunction in mice for Cognitive Enhancement

Authors: *M. SINGH, P. SHARMA, T. GURJEET SINGH;
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Abstract: Neuropharmacological Exploration: Novel chalcone based small molecules ameliorate STZ induced memory dysfunction in mice for Cognitive Enhancement

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Background: one of the leading causes of dementia is Alzheimer's disease, which initiated via plethora of biochemical alterations in brain of which Cholinergic, oxidative stress, and advance glycation end products (AGEs) have been identified as key mediators. Thus, the development of drugs targeting these pathways may help in managing AD.
Method: Novel aminoalkylchalcone based molecules were designed and synthesized using aldol condensation method. *In silico* predication analysis was taken to determine the interactions of synthesized drugs with acetylcholinesterase. Memory enhancing effects were determined *in-vivo* for most potent molecule against Streptozotocin induced memory deficit in mice. Possible mechanisms were studied by determining various brain biochemical parameters.
Result: The ten aminoalkylchalcones were synthesized and showed strong interactions with crucial amino acids of target protein. Additionally, syntheses molecules showed strong AChE, DPPH and AGEs inhibitory activity determined *in vitro*. Furthermore, these novel compounds reversed STZ induced cognitive deficit (Morris water maze test) as well as oxidative stress, cholinergic hyperactivation and AGEs formation.
Conclusion: Aminoalkylchalcones had potential to improve the cognitive functions via improving cholinergic transmission and reducing oxidative stress and AGEs. Thus, these potential molecules could be taken for further studies including toxicity evaluation to develop them as anti-Alzheimer's disease drugs.
Keywords: Dementia, Alzheimer's disease; AChE, AGEs, Cholinergic

Disclosures: M. Singh: None. **P. Sharma:** None. **T. Gurjeet Singh:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

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Program #/Poster #: PSTR369.09/V38

Topic: H.08. Learning and Memory

Title: An inverse agonist of the 5-HT2A receptor offers non-hallucinatory modulation of fear memory extinction in adult C57BL/6J mice

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Abstract: Post-traumatic stress disorder (PTSD) and severe anxiety can develop after experiencing a scary, shocking, or life-threatening event. Fear extinction is a neurobiological

process in which new learning inhibits the expression of persistent fear responses acquired after the initial traumatic event. Identifying the cellular and molecular mechanisms supporting extinction memory hold promise for the development of novel PTSD treatments. Stimulation of 5-hydroxytryptophan (5-HT) 2A receptors (5-HT2AR) by hallucinogenic agonists facilitates fear extinction in humans and rodents. Hallucinogenic and non-hallucinogenic agonists activate 5-HT2AR differently. MDL11,939, an inverse agonist of 5-HT2AR, antagonizes the effect of hallucinogenic agonists on fear extinction. Another 5-HT2AR inverse agonist, pimavanserin, given in combination with a selective 5-HT reuptake inhibitor (SSRI) facilitated fear extinction in rodents. Thus, drugs modulating the 5-HT2AR without hallucinatory effect may be efficacious for PTSD as facilitators of fear extinction. We hypothesize that inverse agonists of 5-HT2AR can interact with the form of 5-HT2AR targeted by hallucinogenic agonists. To test this hypothesis, adult male C57BL/6J mice underwent fear conditioning comprising presentation of 3 pairings of a tone CS with a 0.5 mA footshock in Context A. In Exp't 1, 24 h later, mice received 5% DMSO vehicle or MDL11,939 (0.5 mg/kg) and 30 min later received extinction training in Context B comprising 7 non-reinforced CSs with a 120-s ISI. All mice received a second extinction training session the following day. In Exp't 2, 24 h after fear conditioning, mice received 5% DMSO vehicle or MDL11,939 (0.5 mg/kg) and 30 min later received 20 non-reinforced CSs with a 5-s ISI. Extinction was repeated 24 and 48 h later. Preliminary results from Exp't 1 indicate that MDL11,939-treated mice exhibited decreased CS-elicited freezing during the second extinction session as compared to vehicle-treated mice. Modulating 5-HT2AR with MDL11,939 may offer insight into how the receptor influences fear extinction and elucidate the role of the receptor in fear processing.

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Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

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Program #/Poster #: PSTR369.10/W1

Topic: H.08. Learning and Memory

Support: Trone Family Eminent Scholarship

Title: Mice Use a Hippocampal-Dependent Strategy to Solve Serial Feature Negative Problems

Authors: *N. GHASEM ARDABILI[1], J. PETTIFORD[2], A. HYDE[3], M. MALIK[4], C. AIROSUS[2], A. L. RILEY[5], T. DAVIDSON[6];
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Abstract: Background: Prior research shows that rats can solve nonspatial serial feature negative (sFN) discriminations, and simple discrimination (SD) problems, when both are trained concurrently. Furthermore, previous studies indicate that the solution of the sFN problem, but not the SD problem, depends on the functional integrity of the hippocampus. The present research aims to determine if mice, like rats, also solve the sFN problem using a hippocampal-dependent (HiP-D) strategy. Experiment 1 used transfer tests to assess the strategy used by mice to solve the sFN problem. In addition, the impact of cocaine (Experiment 1) and a high-fat, high-sugar (HFHS) diet (Experiment 2) on the performance on the sFN and SD problems was also assessed. Showing that mice, like rats, can solve the sFN problem using a HiP-D strategy would provide researchers with greater flexibility when selecting genetic or other research tools to study HiP-D memory. **Methods:**In Experiment 1, 14 male and 16 female mice were trained concurrently on both sFN and SD problems until reaching asymptote. After 18 daily cocaine injections (20 mg/kg, ip), performance on both tasks was probed. Subsequent summation and retardation tests were used to see if performance observed in the sFN problem relied on HiP-D modulatory learning or on a hippocampal-independent (HiP-I) simple associative strategy. In Experiment 2, mice (16 of each sex) were trained on both problems and then given ad libitum HFHS diet for 12 days, before their performance on both tasks was assessed. **Results:** In Experiment 1, mice acquired both the sFN and SD tasks, responding less on nonreinforced compared to reinforced trials. Probe tests indicated that the mice, like rats in previous studies, used a HiP-D strategy to solve the sFN problem. However, neither sFN nor SD performance was altered by cocaine administration (Experiment 1). In contrast, sFN, but not SD performance was impaired by consumption of HFHS (Experiment 2). **Discussion:** Mice, like rats, can acquire concurrently trained sFN and SD discriminations. Experiment 1 provided evidence that sFN discrimination was most likely based on a HiP-D modulatory learning strategy and not on HiP-I simple associative learning. Although cocaine had no apparent effect on performance based on either strategy, similar to previous studies with rats, ad libitum HFHS consumption selectively impaired performance on the HiP-D sFN problem The results indicate that for mice, like rats, performance of the sFN discrimination problem depends on the functional integrity of the hippocampus. Thus, the sFN problem can be used to study HiP-D nonspatial memory in mice, as well as in rats.

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Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

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Program #/Poster #: PSTR369.11/W2

Topic: H.08. Learning and Memory

Support: PAPIIT-UNAM IN209621
PAPIIT-UNAM IN207224

Title: Consolidation of cued water maze memory correlates with enhanced striatal mitochondrial activity

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Abstract: Stressful experiences tend to form lasting memories, due to enhanced neural plasticity mechanisms linked to glucocorticoid hormones. The dorsal striatum participates in the consolidation of stressful memories, in tasks such as the cued water maze task. An important aspect of neural plasticity is the mitochondrial activity that is related to energy production and signaling mechanisms for functional and morphological neuronal adaptations. It has been reported that brain mitochondrial activity can be enhanced by corticosterone and depending on the glucocorticoid receptor activation, and, that striatum functions are vulnerable to changes in mitochondrial processes. We hypothesized that training in the cued water maze would induce an increase in corticosterone levels and mitochondrial activity (mitochondrial membrane potential, calcium content) of the dorsal striatum, and that this increment could be of importance for memory consolidation of the task. We evaluated plasma and striatal corticosterone levels, mitochondrial activity, determined with the florescent probes for mitochondrial membrane potential and calcium content, in brain slice with the dorsal striatum of rats trained in the cued water maze and euthanized at different times after training (0.5, 1.5 and 6.0 h). We also analyzed the effect of post training inhibition of striatal mitochondrial activity by OXPHOS complex 1 inhibitor Rotenone on the consolidation of the task. We found that cued water maze induced an increase in corticosterone levels and a time dependent increment of mitochondrial membrane potential and mitochondrial calcium content in the dorsal striatum, Rotenone administration facilitated retention which was not avoided by antagonizing the glucocorticoid receptor. Altogether our results suggest that the enhancement of dorsal striatum mitochondrial activity is relevant for cued water maze consolidation, this effect relates contextually with an elevation of CORT in plasma and dorsal striatum but was independent from glucocorticoid receptor activation. We acknowledge the technical assistance of Nydia Hernandez, Norma Serafin, Olivia Vázquez-Martínez, Andrea C. Medina, Bernardino Osorio, Martín García, Ramón Martínez and Nuri Aranda. This project was supported by Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica, Dirección General de Asuntos del Personal Académico, Universidad Nacional Autónoma de México (Grants PAPIIT-UNAM IN209621 and IN207224).

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Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

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Topic: H.08. Learning and Memory

Support: 18/1/2022/IDUB/I3b/Ag
2020/39/I/NZ4/02070

Title: Non-invasive pupil dynamics signal coincident high frequency oscillations in the intracranial EEG associated with memory recall

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Abstract: High-frequency oscillations (HFOs) in the gamma, ripple, and fast ripple frequency ranges of intracranial EEG (iEEG) are related to memory and cognitive processing. HFOs, however, can only be recorded on selected intracranially implanted electrode contacts through invasive surgical procedures. Eye tracking, on the other hand, offers non-invasive measures correlated with memory and cognition. Thus, we hypothesized that pupillometric measures will correlate with HFO activities and indicate memory processing non-invasively. This study involved drug-resistant epilepsy patients (N=18) who completed a series of cognitive tests, including a free recall verbal memory task. In this task, participants were required to read a list of words and, after a set of arithmetic operations, recall as many words as possible. Eye tracking and iEEG signals were extracted from a 2-second window around the beginning of recalled word verbalization. HFOs were detected and analyzed in time to identify coincident occurrences across multiple electrode contact channels, indicating synchronous discharge across multiple brain regions. Pupil position and size were estimated around each coincident HFO event within a 0.2 second range. Pupil size revealed a rapid dilation immediately preceding memory recall, which closely paralleled in time with an increased rate of HFO detections. This pattern of pupil dilation related to memory recall was present also on a micro-scale of detecting individual coincident HFO events. The pupil started increasing a few milliseconds before the onset of the synchronous HFO discharge across the brain. Our study provides evidence for a non-invasive pupillometric signal that is tightly correlated in time with intracranial electrophysiological activities underlying successful memory recall. The invasive and non-invasive measures showed similar temporal patterns and were aligned within a millisecond range of brain-wide coincident bursts of high frequency oscillations. The results suggest that pupil size may reflect the cognitive and neural processes associated with memory retrieval. This alignment between eye movements and neural activity highlights the potential utility of non-invasive eye tracking techniques as a proxy for monitoring momentary cognitive states, particularly in contexts where direct measurements of neurophysiological activities are not feasible or practical.

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Poster

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Title: Dynamics of memory retrieval and forgetting shaped by histamine neuronal activity

Authors: Y. MORISHITA[1], Y. TAKAMURA[1], K. NISHIMURA[2], Y. YOKOI[1], R. IZUTSU[1], N. HITORA-IMAMURA[3], M. MINAMI[4], ***H. NOMURA**[1];
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Abstract: Memory retrieval involves more than the mere reactivation of memory traces; it is also shaped by brain state mechanisms that remain incompletely understood. Despite that identical cues are presented, the ability to retrieve memories can fluctuate, with memories sometimes accessible and sometimes not. This suggests that neuronal activity prior to memory cues might significantly influence memory retrieval. Histamine, primarily produced in the tuberomammillary nucleus (TMN) neurons, is released throughout various brain regions and plays a significant role in learning and memory, as well as in wakefulness, motivation, and energy balance. Notably, histamine is a potential key modulator of memory retrieval. We have previously demonstrated that antagonists/inverse agonists of histamine H_3 receptor stimulate the histaminergic nervous system by increasing histamine synthesis and release, thereby enhancing the retrieval of object recognition memories. Given that brain histamine originates from the TMN histamine neurons, their activity could be linked to the efficiency of memory retrieval. Here, we employed fiber photometry, optogenetics, and Ca^{2+} imaging to explore how histamine neuronal activity modulates memory retrieval in mice. We observed that histamine neurons display spontaneous activity fluctuations independent of external stimuli and that this activity correlates with successful retrieval of cue-reward memory. Our closed-loop system for cue-reward presentation demonstrated that cues presented during periods of heightened histamine neuronal activity improve memory retrieval. Moreover, optogenetic inhibition and activation of histamine neurons reduced and promoted the efficiency of memory retrieval, respectively. These findings indicate that histamine neuronal activity modulates fluctuations in memory retrieval.

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Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

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Program #/Poster #: PSTR369.14/W5

Topic: H.08. Learning and Memory

Support: Netherlands Ministry of Defense
TNO

Title: Enhancing human learning: Transcutaneous cervical vagus nerve stimulation (ctVNS) improves learning on a visual detection task

Authors: D. RAVESTEIN[1], L. HENDRIKSE[1], G. VELDHUIS[1], H. J. PENNINGS[1,2], *Y. M. FONKEN[1];
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Abstract: Modern technological advances place pressure on people to constantly develop and deepen skills and knowledge ensuring readiness for new challenges in the work-context. New promising developments aimed at increasing learning processes could make a difference in the functioning of individuals and society. Especially in light of external factors, such as wartime or large-scale public health emergencies like the recent COVID-19 pandemic, which heighten the urgency for workers to swiftly acquire fresh skills and knowledge. Numerous external learning enhancements, like adaptive and technology-enhanced learning, have been studied. Exploring internal learner interventions could further optimize learning. A promising intervention to enhance or accelerate learning processes is transcutaneous cervical vagus nerve stimulation (ctVNS) McIntire and colleagues (2019) showed that applying a small current non-invasively to the cervical branch of the vagus nerve accelerates and improves learning. The current study aims to replicate these findings to test the robustness of the effect found by MCIntire et al. In our study, 22 participants were trained in a specialized visual detection task in which they learned to recognize specific vehicles in Synthetic Aperture Radar (SAR) images over the course of four days. On each day, participants received either real ctVNS or sham ctVNS before and after the training task, using the gammaCore Sapphire™ device by Electrocore. Participants were assessed on performance on the SAR task after each training. In addition, retention of the learned task was assessed one day, one month and two months later. Our preliminary results show that ctVNS significantly improves learning performance (MANOVA: $F(4, 138) = 3.55$, $p = .008$; Wilks' $\Lambda = 0.907$). Although these results are preliminary, they show that ctVNS has the potential to improve learning performance on a visual detection task. These preliminary results seem to replicate the main finding of McIntire and colleagues (2019), suggesting that the effect of ctVNS on learning is a robust effect. Potential mechanisms behind this effect could be ctVNS inducing an increase in alertness and neuroplasticity through indirect stimulation of the locus coeruleus. Overall, ctVNS seems a promising method to boost learning and memory performance.

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Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

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Topic: H.08. Learning and Memory

Support: Wellcome Trust Early Career Award - 226333/Z/22/Z
Oxford University Press John Fell - AVD00790

Title: Neurophysiological Principles of Reward

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Abstract: Across species, dopamine is critical for encoding learned associations. Although recent advances in connectomics and single-cell transcriptomics have provided key information about the neural architecture and molecular features of individual dopaminergic neurons, what remains to be understood are the physiological principles governing dopaminergic neurons on an equivalent single neuron level. And although these anatomical and molecular features suggest dopaminergic neurons exhibit a high degree of heterogeneity, there is little known about the diversity and flexibility of physiological computations dopaminergic neurons perform. In Drosophila melanogaster, dopaminergic neurons project to a region known as the Mushroom Body, which is the centre of associative learning and memory in the fly brain. Subsets of these dopaminergic neurons are known to be important for encoding food-related memories, these are known as the a1 dopaminergic neurons (8 neurons per hemisphere). By performing dual in-vivo whole cell patch clamp electrophysiology across a1 dopaminergic neurons and their postsynaptic partners, we have uncovered basic physiological principles of reward encoding. First, a1 dopaminergic neurons exhibit three distinct spiking patterns that are synchronized across ipsilateral a1 dopaminergic neurons. We find evidence that neurons can transition between different spiking patterns and can exhibit two spiking patterns at the same time during these transition states. Second, we find evidence that a1 dopaminergic neurons have two spike initiation zones (SIZ) that are subject to different neuromodulatory inputs and shifts in spiking patterns may arise from differential activation or inhibition of the two SIZs. Third, outputs of the a1 dopaminergic neurons, known as the a1 Mushroom Body output neurons exhibit a high degree of synchronization of activity across ipsilateral pairs. We find that this is coordinated by gap junctions between a1 Mushroom Body output neuron pairs and that RNAi-mediated knockdown of subunits forming these gap junctions interferes with olfactory appetitive sugar memory formation. Our work reveals that the physiological properties of neurons in reward

circuits are more complex and variable than previously considered. By understanding how these physiological complexities permit the assembly of a reward memory, we are establishing the mechanistic basis of how reward is encoded in the brain

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Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

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LD PhD CONACYT Grant No. 850282

Title: Propranolol and mifepristone modify cognitive flexibility in innate anxious and resilient rats

Authors: *L. DÍAZ[1], A. UGARTE[2], C. CORTES[3], J. R. EGUIBAR, Sr.[4];
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Abstract: Cognitive flexibility is the adaptation of behavior in face of a changing environment, in this context the release of stress hormones noradrenaline and glucocorticoids during environmental challenges have deleterious effects on this capacity. Therefore, the antagonism of adrenergic and glucocorticoid receptors can ameliorate the above-mentioned neuronal effects. We inbreed two sublines from Sprague-Dawley (SD) rats, the low- and high-yawning sublines LY and HY, respectively. LY with 2 yawns/h, while the HY with 20 yawns/h. In addition, LY and HY males express an anxious and resilient behavioral pattern, respectively, because they perform differently in the open-field arena and in the light-dark box. The aim of this study was to determine the effect of β adrenergic and glucocorticoid receptor (GR) antagonism on cognitive flexibility. To accomplish that, we administered to SD, LY and HY males (8 rats/group) three doses of propranolol, an α/β adrenergic blocker; 0.5, 1.0 and 2.0 mg/Kg; and mifepristone, a GR antagonist, with 10 mg/Kg, administered subcutaneously 30 minutes before and immediately after training, respectively. All subjects were trained in eight consecutive trials in a Barnes maze with the escape box in a fixed position, cognitive flexibility was measured 24 hours and 7 days after this, in the absence of the escape box. In both evaluations we measured the time spent in the learned position of the escape box, and the time spent in the zone without the escape box named the opposite one. Our results showed that at 24 h evaluation, 2 mg/Kg of propranolol improved cognitive flexibility in Sprague-Dawley rats ($P<0.05$). However, in LY subline a lower dose was needed 1 mg/Kg to produce this effect ($P<0.01$). At 7 days evaluation, SD males explored more

the opposite position when administered with 0.5 and 1 mg/Kg of propranolol. In the same evaluation, LY and HY, 2 mg/Kg of the β adrenergic blocker increased the cognitive flexibility (LY: $P<0.01$, and HY $P<0.05$). In SD and HY rats the administration of 10 mg/Kg of mifepristone raised the exploration in the opposite zone with respect to the learned one, in both evaluations short-term ($P<0.05$) and long-term ($P<0.01$). Mifepristone did not improve cognitive flexibility in anxious LY males ($P>0.05$), with poor cognitive flexibility when compared with SD group ($P<0.05$). We conclude that the blocking of α/β adrenergic receptors with propranolol improved the cognitive flexibility in all tested groups, and because mifepristone did not change this capacity in LY subline with respect to HY and SD groups, it is possible that it can have differences of glucocorticoid receptors in relevant brain areas such as the hippocampus or amygdala.

Disclosures: L. Díaz: None. **A. Ugarte:** None. **C. Cortes:** None. **J.R. Eguibar:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.17/W8

Topic: H.08. Learning and Memory

Support: FWO 1299924N

Title: Learning-induced modulation of single neurons in the human medial occipital and temporal lobes

Authors: *M. ARMENDARIZ[1], G. KREIMAN[2];
[1]Harvard Med. Sch. / Boston Children's Hosp., Cambridge, MA; [2]Harvard Med. Sch., Boston, MA

Abstract: Humans can swiftly learn to recognize new objects with one or a few exposures. This rapid learning process necessitates the formation of enduring neural signatures to enable subsequent recognition. How does the brain encode this newly acquired experience? To investigate this question, we recorded 1104 single neuron activity in medial occipital and temporal brain areas of human patients during an image recognition task involving learning. In this task, participants were shown sequences of images and instructed to report whether they recognized the identity of the depicted objects. Images consisted of grayscale pictures and corresponding two-tone black and white (Mooney) counterpart images. Because Mooney images are almost unrecognizable without prior learning, learning trials were used to facilitate recognition. Consequently, participants showed poor recognition of Mooney images before learning, with their identities becoming highly discernible after few learning trials. Neural activity was modulated by learning at the single unit level across areas of the medial occipital and temporal lobes. Following learning, these neurons changed their firing patterns in response to Mooney images to resemble those of the grayscale images. These findings were particularly

evident when examined at the population level. Using population decoding, we were able to discriminate between pre- vs. post-learning images (which are identical) with an accuracy of up to 75%. Overall, decoding accuracy was higher during a later stage (300-700ms) after the image onset, suggesting a greater influence of visual input at earlier decoding stages and the need for additional processing to support recognition. Finally, we used a transfer learning approach to assess object identity generalization. Decoding the identity of grayscale images only generalized to post-learning Mooney images. Generalization was observed in medial occipital and temporal areas and required additional processing time to reach peak decoding. Taken together, our results provide evidence of learning-induced effects in the medial occipital and temporal areas, where modulation of single neuron firing rates reflects recently acquired knowledge. Furthermore, our findings suggest the necessity of additional processing beyond bottom-up visual input representations to support recognition following recent learning.

Disclosures: M. Armendariz: None. **G. Kreiman:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.18/W9

Topic: H.08. Learning and Memory

Support: NIH Grant RO1 NS 113078-01

Title: Activity of the monkey dentate nucleus during visuomotor association learning

Authors: *A. IPATA, V. SONI, M. E. GOLDBERG;
Neurosci., Columbia Univ., New York, NY

Abstract: Recent work has shown that the cerebellum is involved in cognitive as well as motor processing. We have recently trained monkeys to perform a visuomotor association task. The monkeys learn to associate one of two symbols with a left-hand movement and the other to a right-hand movement. They are overtrained on a single pair of symbols, and when they are performing at a rate close to 100%, they are shown a pair of fractal symbols they have never seen. It takes them 40 to 80 trials to learn which is the right-hand symbol and which is the left. The simple spikes of Purkinje cells (PCs) in Crus I and Crus II become sensitive to reward when monkeys learn the associations of the new symbols, but not when they fail to receive a reward when they respond to overtrained symbols (Sendhilnathan et al., 2020). The reward sensitivity of the simple spikes approaches zero as the monkeys learn the task. The kinematics of the movement do not change during the visuomotor association task. Inactivation of Crus I and II impairs learning new visuomotor associations but does not change the monkeys' responses to overtrained symbols, nor does it affect the kinematics of the responses (Sendhilnathan et al. 2024). Crus I and II project to the dentate nucleus (DN), which integrates signals from multiple PCs before relaying them to the thalamus and thence to the cortex. The DN output to the primary

motor area originates from more dorsal and rostral parts, whereas more ventral parts project to cerebral areas related to cognitive functions, such as the dorsal prefrontal cortex and pre-PMD. The DN receives projections from the inferior olive via climbing fibers, and many sensory and motor projections from mossy fibers. During visuomotor association, we find that neurons in the dorsal DN respond to movements of one hand, unlike PCs in Crus I and II which respond to movements of both hands, suggesting that dorsal dentate is more likely to have a predominantly motor function, in keeping with its anatomical projections. Neurons in the ventral dentate resemble the simple spikes in Crus I and II. They respond to movements of both hands both during the overtrained task and during learning. During learning, but not during the overtrained task, they also respond to success or failure of the prior trial. On the population level, the dentate reward responses precede the Purkinje cell reward responses, suggesting that even though the PCs project to the dentate they do not provide the reward-related signals. These findings hold significant implications for understanding the dynamics of information processing within the cerebellum and its role in visuomotor learning and memory formation.

Disclosures: A. Ipata: A. Employment/Salary (full or part-time):; Columbia University. **V. Soni:** A. Employment/Salary (full or part-time):; Columbia University. **M.E. Goldberg:** A. Employment/Salary (full or part-time):; Columbia University.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.19/Web Only

Topic: H.08. Learning and Memory

Support: CIHR grant 109219

Title: Isoflurane anesthesia induced sex-related differences in gene expression

Authors: R. TADAVARTY[1], T. MARIAM[1], S. SINHA[1], G. GIAEVER[1], C. NISLOW[1], ***P. SOJA**[2,3];
[1]Fac. of Pharmaceut. Sci., Univ. of British Columbia, Vancouver, BC, Canada; [2]Univ. of British Columbia, Vancouver, BC, Canada; [3]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

Abstract: Exposure to general anesthesia (GA) can affect cognitive performance and increase the risk of dementia, leading to post-operative cognitive dysfunction (POCD). POCD can last up to several months or years. Surprisingly, males but not females are more vulnerable to POCD; the reason(s) behind this discrepancy are not known. At the cellular level, we recently found that prolonged exposure (5h) to surgical (relative 1%) or deep (relative 5%) levels of isoflurane (ISO) anesthesia affect long-term plasticity of population excitatory postsynaptic potentials in the CA1 region of the hippocampus, in opposing ways. The effect of GA on synaptic plasticity is sex-dependent, with male rats displaying a greater propensity for long-term alterations, compared to

females. Whether or not alterations in gene expression patterns precede these distinct changes is currently unknown. Since the expression of synaptic plasticity and its sustenance is critically dependent on gene expression, we hypothesized that a prolonged exposure to ISO anesthesia induces selective changes in gene expression in male vs female rats. In all our experiments, cortical EEG was continuously recorded to ensure a constant anesthetic depth. Adult male or female SD rats were initially anesthetized in an induction chamber, their trachea intubated and head mounted in a stereotaxic frame. Cortical EEG was recorded using stainless steel screw electrodes positioned in S1 bilaterally. After 5h exposure to surgical or deep ISO anesthesia, S1 cortical tissue was dissected and RNA-seq was used to quantify changes in the transcriptome. Differential expression analysis was performed on these datasets to identify cohort-specific changes. We analyzed the expression of ~13000 genes. Prolonged exposure to surgical or deep levels of ISO anesthesia induced a significant up- or down- regulation in a smaller proportion of genes in males compared to females. Around 33 vs 211 genes were significantly altered compared to respective controls in male vs female rats at surgical levels, whereas 112 vs 629 genes were altered under deep ISO anesthesia. Furthermore, gene ontology enrichment analysis indicated that differentially expressed genes affect aspects of synaptic transmission, protein phosphorylation, and long-term memory. The sex-dependent changes in gene expression following GA exposure may therefore underlie the differential expression of behavioral POCD between males and females.

Disclosures: R. Tadavarty: None. **T. Mariam:** None. **S. Sinha:** None. **G. Giaever:** None. **C. Nislow:** None. **P. Soja:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.20/W10

Topic: H.08. Learning and Memory

Support: 5R24AG073078-03

Title: High fat diet facilitates acquisition of discrimination learning and alters glycerophospholipid metabolism

Authors: *D. WANG[1], E. IREWOLE[2], L. BAYS[3], M. SMITH[3], B. G. SCHREURS[2]; [1]West Virginia Univ., Sch. of Med., Morgantown, WV; [2]Neurosci., West Virginia Univ., Morgantown, WV; [3]West Virginia Univ. - PhD in Neurosci., Morgantown, WV

Abstract: Previous reports have shown an association between a western diet and poor cognitive performance. This study was designed to explore whether feeding a high fat diet (HFD: 5% lard and 5% soy oil) for 20 weeks affected discrimination and discrimination reversal learning and, if so, what the underlying mechanism might be. After 20 weeks on the HFD or a normal control diet, 30 rabbits [n=18 (9 Males and 9 Females), 12 (6 Males and 6 Females), for HFD and

Control group, respectively] received one day of adaptation, 20 daily sessions of two-tone discrimination (1 kHz tone CS+ followed by air puff and 8 kHz tone CS- not followed by air puff), and then a rest day, followed by 40 daily sessions of discrimination reversal (8 kHz CS+ and 1 kHz CS-). Compared to rabbits fed a regular chow diet, rabbits fed with HFD had better discrimination evidenced by higher levels of responding to 1 kHz CS+ and lower levels of responding to 8 kHz CS-. These same HFD-fed rabbits exhibited lower levels of responding to 1 kHz CS- but similar levels to 8 kHz CS+ at the end of discrimination reversal, suggesting they were better able to acquire the new relationship between the two tones by inhibiting responding to the 1-kHz tone CS-. Widely targeted Metabolomics analysis identified 1492 metabolites in the hippocampus, and Principal Component Analysis revealed significant changes in 149 differential metabolites between the HFD and Control group, Interestingly, 118 were downregulated compounds and included glycerolipids, glycerophospholipids, amino acid and its metabolites, and fatty acyls. The information from a Hierarchical Cluster Analysis clearly separated hippocampal samples from HFD and Control group, indicating the significant heterogeneity in hippocampus between HFD and Control group. KEGG enrichment analysis showed glycerophospholipid metabolism (ko00564) was significantly enriched in the HFD group. In summary, our data showed long-term feeding of HFD facilitated discrimination learning and reversal, which may be mediated by HFD induced alterations in glycerophospholipid metabolism pathways in rabbits.

Disclosures: D. Wang: None. **E. Irewole:** None. **L. Bays:** None. **M. Smith:** None. **B.G. Schreurs:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.21/W11

Topic: H.08. Learning and Memory

Support: Intramural NIH

Title: Sequence regularity determines if early learning gains occur during practice or rest

Authors: *F. IWANE[1,2], E. R. BUCH[3], L. G. COHEN[3];
[1]NIH, Natl. Inst. of Neurolog. Disorders & Stroke (NINDS), Bethesda, MD; [2]Human Cortical Physiology and Neurorehabilitation Section, NINDS, Bethesda, MD; [3]Human Cortical Physiol. and Neurorehabilitation Section, NINDS, Bethesda, MD

Abstract: Skill learning engages explicit and implicit mechanisms. While experimental task designs may emphasize one, the other or both, many real-world skills mirror explicit sequential learning tasks (i.e., learning a piano concerto), where subjects know they will learn pre-determined sequences displayed in front of them [1, 2]. Studies investigating implicit sequence learning typically compare performance between practice of the same repeating sequence with

practice of random sequences, with the difference representing the sequence-specific knowledge acquired. Recent work reported that repetitive practice of a single sequence in a comparatively more implicit serial reaction time (SRT) paradigm elicits surprisingly similar early learning relative to random practice with no repeating sequence structure (Das et al., NCM 2024). Here, we investigated the influence of sequence regularity on early explicit learning over two different experiments. Subjects were instructed to practice a repetitive explicit skill task (skill) and/or random sequences (random) displayed on a screen in the lab (Exp 1, within-individual, n=21) and online (Exp 2, across individuals, n=310). In both experiments, we found that subjects learned over 5-fold more with repetitive practice of the fixed sequence than with practice of random sequences across trials ($p=3.5x10^{-33}$). Performance improvements developed predominantly over periods of rest (offline) in the skill group [2] in contrast to over practice (online) in the random group. Consistent online gains were present in the random condition irrespective of sequence difficulty or tapping speed, in stark contrast to the motor slowing observed in later skill condition trials [2] . Thus, early skill learning, (a) is substantially superior after repetitive practice of the same skill than after practice of random sequences (b) can develop over both practice and rest, depending on practice schedule and (c) may differ depending on the proportion of implicit content. **References: [**1] Karni et al. (1995) *Nature*, 377(6545):155-158. [2] Bönstrup et al. (2019) *Curr Biol*, 29(8):1346-1351 e1344.

Disclosures: F. Iwane: None. **E.R. Buch:** None. **L.G. Cohen:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.22/W12

Topic: H.08. Learning and Memory

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McDonnell Center for Systems Neuroscience
Fondazione Neurone

Title: The Interaction between Eye Movement and Middle Temporal Lobe activity During Visual Exploration: Insights from Electrophysiological Data

Authors: *G. TAN[1], Y. LI[1], Z. LI[2], J. R. SWIFT[3], K. L. WAHLSTROM[4], C. S. INMAN[4], E. C. LEUTHARDT[1], J. T. WILLIE[5], P. BRUNNER[6];

[2]Biomed. Engin., [1]Washington Univ. in St. Louis, Saint Louis, MO; [3]Dept. of Neurosurg., Washington Univ. Sch. of Med., Saint Louis, MO; [4]Psychology, Univ. of Utah, Salt Lake City, UT; [5]Neurolog. Surgery, Sch. of Med., Saint Louis, MO; [6]Dept. of Neurosurg., Washington Univ., St. Louis, MO

Abstract: To optimally process incoming visual information, the neural system must dynamically adjust its activity in response to eye movements. Previous studies have demonstrated the coordination between theta activity in the middle temporal lobe (MTL) and eye movement. Specifically, theta activities represent brain states that are recalibrated through saccades to enhance the encoding of visual information. While it is intuitive that gaze direction should be influenced by prior visual encoding, the mechanisms underlying this process have not been fully elucidated. In this study, we hypothesized that eye movements are guided by the MTL, a critical area for visual encoding and memory retrieval. We concurrently recorded eye movements and intracranial EEG from two neurosurgical patients engaged in a visual encoding task. Consistent with prior findings, we found a significant increase in theta activity in the MTL following image presentation compared to fixation-cross presentation. When compared to the resting-state baseline, theta activity in the MTL following the image presentation fixation cross was higher. In addition, the theta increase persisted throughout the image presentation, suggesting that theta activity represents the visual encoding. Importantly, theta activity was higher after saccades. These findings suggest that theta activity in the MTL represents visual encoding and is modulated by eye movement. Further investigations revealed significant gamma band activity (30 - 70 Hz) within 50 ms of saccade initiation, identified through cluster-level permutation tests ($p < 0.05$). Similar patterns were also present during periods of fixation cross presentation. This gamma activity, characterized by increased local field potentials that precede ocular muscular activities, underscores the MTL's role in timing eye movements. We used a recurrent neural network to predict saccade timing based on MTL activity. The results show that the model (F1 score = 0.16 ± 0.12) predicts unseen data significantly better than at chance (F1 = 0.05 ± 0.03). Altogether, our results suggest the bidirectional modulation between MTL activity and eye movement.

Disclosures: G. Tan: None. **Y. Li:** None. **Z. Li:** None. **J.R. Swift:** None. **K.L. Wahlstrom:** None. **C.S. Inman:** None. **E.C. Leuthardt:** None. **J.T. Willie:** None. **P. Brunner:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.23/W13

Topic: H.08. Learning and Memory

Support: DP2-AG071918
1K99NS136846

Title: Dynamics of hippocampal barcode and place code activity during remote memory recall

Authors: *S. N. CHETTIH, D. ARONOV;
Zuckerman Inst., Columbia Univ., New York, NY

Abstract: Food-caching behavior is an emerging model system to identify neural mechanisms underlying episodic memory. Chickadees in particular form single-shot, hippocampal-dependent memory of their caches in the wild and in laboratory settings. During caching, chickadee hippocampal neurons generate sparse, transient representations of individual caching events. These neural 'barcodes' are orthogonal to the place code, reactivate during cache retrieval, and thus may be neural signatures of individual memories. However, it is not enough for a memory signature to reactivate only when the bird is about to retrieve a cache; it should also be able to activate long before actual retrieval and bias future behavior towards retrieving the recalled item. Do barcodes reactivate remotely in this manner? It is furthermore unclear how place activity might support the processes of memory recall and/or navigation to the location of a recalled item. Does place activity precede and support reactivation of a barcode, or does place activity follow barcode reactivation and signal the remembered location? Resolving these questions would clarify specific mechanisms by which hippocampal memory guides behavior.
We designed a novel behavioral arena for food caching based on a radial arm maze. Chickadees cached in sites at the end of each maze arm and later retrieved these caches to eat. The radial arm design forced chickadees to make decisions in the center of the arena, far from the cache sites and long before the chickadee interacted with these sites. We used high-speed multi-view videography to reconstruct 3D posture and gaze location throughout behavior. Retrievals were often preceded by deliberative periods, where a chickadee made gaze saccades between multiple options before it committed to traversing a path to a cache site. We recorded from large populations of hippocampal neurons during free behavior using a customized, lightweight drive for silicon probes. As in previous work, we observed barcode activity during caching in our new arena. We also found that hippocampal neurons encoded current location as well as gaze location. Ongoing work is characterizing the temporal relationship of encoding for current location, gaze location, and barcode activity during deliberative periods.

Disclosures: S.N. Chettih: None. **D. Aronov:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.24/W14

Topic: H.08. Learning and Memory

Support: Beckman Foundation Young Investigator Award
New York Stem Cell Foundation Robertson Neuroscience Investigator Award
NIH Director's New Innovator Award (DP2-AG071918)
Simons Society of Fellows

Title: Interactions between the hippocampus and lateral hypothalamus during dynamic food-caching behavior

Authors: *I. I. C. LOW, D. ARONOV;
Zuckerman Mind Brain Behavior Inst., Columbia Univ., NEW YORK, NY

Abstract: Humans and other animals form “one-shot” episodic memories in an instant, which they can later use to guide their behavior. For example, food-caching birds like the black-capped chickadee can hide thousands of seeds throughout the forest and later return with striking accuracy to the precise location of each hidden seed. To survive, chickadees must not only remember where they have hidden their seeds; they must also make the correct moment-to-moment decisions as to whether to eat or cache them. This interplay between memory and behavior likely depends on precise coordination between the hippocampus, which supports memory formation and retrieval, and downstream regions that guide feeding behavior. We do not yet know what these feeding-related circuits are in the chickadee, but the lateral hypothalamus is an intriguing candidate. This region is known to be important for feeding and food-hoarding behaviors in mammals and birds. It is also bidirectionally and monosynaptically connected to the hippocampus, so it is poised to receive and modulate memory-related signals. Using retrograde tracing, we have identified a compact nucleus of hippocampal neurons that projects to the lateral hypothalamus. Further, using an arena designed to engage natural food-caching behavior in the lab, we have observed behavioral state transitions between feeding and caching modes at a variety of timescales, from seconds to minutes to hours. To determine how the hippocampus coordinates with the lateral hypothalamus across these behavioral transitions, we are using a lightweight, miniaturized microdrive system to obtain silicon probe recordings from the hippocampal projection nucleus during food-caching behavior. To identify which hippocampal signals are relayed downstream, we have adapted antidromic stimulation for use with this system. Using this method, we have tagged hippocampal projection cells to the lateral hypothalamus. In this way, we are characterizing communication between the hippocampus and the lateral hypothalamus during dynamic transitions between feeding and caching. These experiments will provide essential insight into the computations that transform an episodic memory of a cached seed into decisions to retrieve and eat or re-cache that seed.

Disclosures: I.I.C. Low: None. **D. Aronov:** None.

Poster

PSTR369: Learning and Memory: Physiology and Pharmacology

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR369.25/W15

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

Support: NINDS 1SC1NS119056
NIH-NIMHD-5U54MD007592
IDRB Imaging & Behavioral Neuroscience (IBN) facility NIH#

C06OD030148
LSAMP: HRD-1810898

Title: Glycine transporter 1 cell type identification and topographical distribution in the mouse hippocampus

Authors: *L. P. MONTES[1], R. A. PEREZ[1], I. A. GONZALEZ[1], L. JIAO[1], M. MIRANDA-ARANGO[2];
[1]Biol. Sci., The Univ. of Texas at El Paso, El Paso, TX; [2]Dept. of Biol. Sci. and Border Biomed. Res. Ctr., The Univ. of Texas at El Paso, El Paso, TX

Abstract: Glycine is regulated by two glycine transporters, glycine transporters 1 and 2 (GlyT1 and GlyT2, respectively). The expression of GlyT2 has always been associated with neurons and GlyT1 with glial cells, except for neuronal expression of GlyT1 in the amacrine cell layer of the retina. Furthermore, it has been suggested that epileptic rodents had overexpression of GlyT1 in the dentate gyrus (DG). Even though the hippocampus is one of the most studied areas, GlyT1 expression patterns within its subregions have not been deeply studied. The focus of this project is to identify GlyT1-positive cell types in regions of the hippocampus. To do so, we utilized a GlyT1-Cre mouse knock-in line crossed with different reporter lines Ai14 tdTomato (tdTom) and Ai75 nuclear localization signal tdTom (nls-tdTom). Immunohistochemistry assays were performed using different cell markers such as neuronal nuclear protein (NeuN) and glial fibrillary acidic protein (GFAP). Nissl staining was performed in adjacent tissue to identify the subregions of the hippocampus, and using the *Allen Reference Atlas* (*ARA*), boundaries were delineated. Different regions of the hippocampus, such as the Ammon's Horn (CA) field CA1, CA3, and DG were analyzed along the rostrocaudal axis to determine the GlyT1 expression patterns. Preliminary data from the GlyT1/Ai14 showed cells with tdTom and NeuN in several areas of the CA region and the dentate. Additionally, colocalization between tdTom and GFAP was present in different layers of the DG, and CA3. The topographical distribution of GlyT1-positive neurons and glial cells can be used to elucidate glycinergic circuits within the hippocampus which is of pharmacological interest in treating epilepsy.

Disclosures: L.P. Montes: None. **R.A. Perez:** None. **I.A. Gonzalez:** None. **L. Jiao:** None. **M. Miranda-Arango:** None.

Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

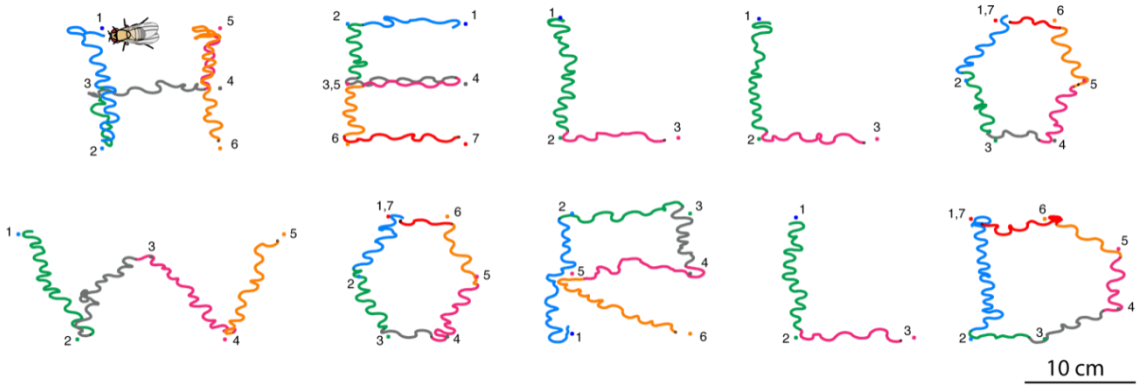
Program #/Poster #: PSTR370.01/W16

Topic: H.09. Spatial Navigation

Title: The fruit fly, Drosophila melanogaster, as a micro-robotics platform

Authors: K. IWASAKI[1], ***A. RAYSHUBSKIY**[1,2];
[1]Rowland Inst. at Harvard Univ., Cambridge, MA; [2]Harvard Univ., Cambridge, MA

Abstract: Engineering small autonomous agents capable of operating in the microscale environment remains a key challenge, with current systems still evolving. Our study explores the fruit fly, *Drosophila melanogaster*, a species adept at microscale interaction, as a biological platform for micro-robotics. Initially, we focus on remotely directing the walking paths of fruit flies in an experimental arena. We accomplish this through two distinct approaches: optogenetic modulation of the fruit fly's olfactory system and harnessing its opto-motor response. These techniques facilitate reliable and repeated guidance of flies between arbitrary spatial locations. We demonstrate that it is possible to guide flies along predetermined trajectories, enabling them to scribe patterns resembling textual characters through their locomotion (the example below is 'written' by a single fly). We extend this control to group behaviors in shared spaces and navigation through constrained maze-like environments. We further use our guidance technique to enable flies to carry a load across designated points in space, which helped establish the upper bound on their weight carrying capabilities. We investigate the enhancement of olfactory-guided navigation through the additional optogenetic activation of various olfactory approach-promoting mushroom body output neurons. Beyond expanding tools available for micro-robotics, this work can provide insights into the neurological basis of behavior in fruit flies.



Disclosures: K. Iwasaki: None. **A. Rayshubskiy:** None.

Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.02/W17

Topic: E.04. Voluntary Movements

Support: U01NS131438
R00NS114179

Title: Exploring the role of a premotor cell type for active sensor control in Drosophila

Authors: *O. M. NUNN, M. P. SUVER;
Biol. Sci., Vanderbilt Univ., Nashville, TN

Abstract: An animal's nervous system enables it to detect and respond to stimuli to navigate its environment. To enhance sensory acquisition, animals can actively position sensors, altering how they extract information from the external world. However, active sensing, and movement in general, produces stimuli that feeds back onto these same sensory systems - requiring mechanisms for integrating predictive motor signals with externally-generated sensations. Despite the importance of these mechanisms for guiding coordinated behavior, the cellular and circuit basis of motor control and sensation during active movements are not fully understood. The *Drosophila* antennae are actuated by a set of four muscles at their base and house the largest mechanosensory organ in the animal, which enables active sensing. Additionally, the fruit fly's surplus of genetic tools, publicly available connectomics resources, and their robust behavior in a lab environment provides an excellent model for investigating these neural mechanisms. Here, I use optogenetics, electrophysiology, and machine-learning assisted antennal tracking to determine how mechanosensory information controls motor output in the *Drosophila* antenna. Previous work showed that a class of antennal mechanosensory and motor center projection neurons contribute to an afferent sensory pathway responsible for the linear encoding of wind direction. However, connectomic data reveals that these neurons synapse onto antennal motor neurons, suggesting a role beyond mechanosensory afference. Further, their optogenetic activation produces ventral antennal deflections, providing additional evidence for a role in controlling antennal movements. To measure the relative influence of mechanosensory input during active movements, I am using whole-cell patch clamp electrophysiology to record changes in neural activity in the presence and absence of mechanosensory input in intact, behaving flies. Together, this work aims to uncover the functional logic of a cell type encoding sensory and motor information, and how it contributes to a circuit controlling the position of an active sensor.

Disclosures: O.M. Nunn: None. **M.P. Suver:** None.

Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.03/W18

Topic: H.09. Spatial Navigation

Support: DP2EY032737
Searle Scholars Program
Sloan Research Fellowship

Title: Connectome and functional imaging reveal visual features critical for navigation in Drosophila melanogaster

Authors: *Y. LAI[1], D. GARNER[1], Z. XIAO[1], L. ROSHKOVAN[1], L. HWANG[1], G. M. RUBIN[2], D. NATESAN[1], S. KIM[1];
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Abstract: For a fly navigating an environment, the heading direction is represented by the activity of compass neurons in the central brain, which receive sensory inputs from a diverse set of neurons, collectively called the ring (ER) neurons. Some ER neurons are part of the anterior visual pathway (AVP) that relays visual information from optic lobes to the compass neurons, and prior studies showed distinct ER populations respond to topographically organized visual stimuli. The specific visual features particular ER neurons encode, however, have not been deciphered. To investigate the anatomical pathways that provide differential visual inputs to each ER population, we used the full adult fly brain EM dataset to densely reconstruct the AVP and trace - at the synaptic level - all connections that converge onto each ER population. We analyzed connectivity and morphology among 3 main neural types involved in the AVP, MeTu (medulla-to-tubercle), TuBu (tubercle-to-bulb), and ER (ring), revealing 4 major pathways that begin from MeTu1-MeTu4 and end at many types of ERs. The spatial connectivity and upstream photoreceptor inputs we uncovered suggest spatially and chromatically distinct processing of visual features. To test this prediction, we leveraged a novel projector-based full-color visual stimulation setup we recently developed. It allows us to image the calcium activity of ER neurons *in vivo* with 2-photon microscopy while presenting the head-fixed fly with colored single-dot stimuli. We observed that ER4d neurons (downstream of MeTu1) responded to vertically elongated visual fields. In contrast, ER2 neurons (downstream of MeTu3) responded to more circular local areas. Further, ER4d were excited by UV, blue and amber light, whereas ER2 were excited by blue and amber but inhibited by UV. These results demonstrate that ER4d and ER2 encode spatial and chromatic visual information conjunctively, consistent with the predictions from our anatomical reconstructions. To further investigate the spatial and temporal dynamics of these neurons, we used random-dot stimuli and developed regression models to describe the neural activities. This analysis revealed different temporal dynamics of excitatory and inhibitory visual inputs to ER neurons. Interestingly, using the activity of other neurons in the same recording sessions as predictors greatly reduced the total number of predictors in the model, without compromising the model's prediction power, indicating lateral interactions among ER neurons. Overall, ER neurons encode multi-feature visual information and they interact to shape the population activity before providing information to the head direction system.

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Poster

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Program #/Poster #: PSTR370.04/W19

Topic: H.09. Spatial Navigation

Support: Visitor support from HHMI, Janelia Research Campus

Title: Mapping the fly connectome onto asymmetric ring attractor networks

Authors: *T. BISWAS[1,2], A. STANOEV[3], S. ROMANI[3], J. E. FITZGERALD[1,2];
[1]Northwestern Univ., Evanston, IL; [2]Theory and Computation, Janelia Research Campus, HHMI, Ashburn, VA; [3]Janelia Res. Campus, Ashburn, VA

Abstract: Ring attractor models are widely employed to describe the head direction system, a crucial component of spatial navigation and path integration. Typically, these models involve a circularly symmetric network of neurons that can encode angular orientations through localized activity bumps that smoothly vary to cover the full 360 degrees. However, this setup doesn't fully mirror biological networks, where asymmetric connectivity amongst multiple nonlinear neuronal populations generates the ring attractor dynamics. Here we propose a theoretical framework for identifying threshold-linear ring attractor networks that continuously encode angular locations even with limited number of neurons as relevant for certain biological settings. Our flexible approach characterizes the solution space of continuous attractor models to facilitate the construction of connectome-constrained ring attractor models. In particular, we scale measured synapse counts from the connectome to derive synaptic weights that exactly map the connectivity matrix onto a continuous ring attractor model in the solution space. We applied our framework to the fruit fly head direction system by incorporating several neuronal populations within the fruit fly central complex. We primarily focused on EPG neurons, which form a ring-like structure in the fly central complex responsible for encoding the fly's orientation through bump-like activity. This activity is thought to be sustained by local excitation among EPGs and distal inhibition from other neuronal populations, such as the Δ7 neurons. Given the asymmetric connectivity between the EPG and Δ7 neurons, an asymmetric effective connectivity between EPG neurons arises when some Δ7 neurons are inactive, thereby breaking the circular symmetry of the effective EPG network. Nevertheless, we could identify three viable connectome-constrained ring networks that predicted different numbers of active Δ7 neurons and distinct EPG activity profiles, offering a means to test and distinguish between the attractor models. These networks also varied in the scale factors associated with the EPG ↔ EPG, EPG ⟶ Δ7, Δ7⟶ EPG, and Δ7 ↔ Δ7 synapses. We therefore explored how the flexibility provided by the continuous attractor's solution space may allow dynamic scale factors to maintain the network in a continuous attractor state despite natural synapse count variation. We additionally showed how coupling to inhibitory populations other than Δ7 neurons can also achieve continuous encoding, underlying the generality of our framework, whose applicability also extends to different model organisms and their connectomes.

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Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

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Program #/Poster #: PSTR370.05/W20

Topic: H.09. Spatial Navigation

Support: HHMI
NIH grant R35NS132252

Title: Drosophila maintain a consistent navigational goal angle for days to weeks

Authors: *J. L. WEISMAN[1], T. L. MOHREN[2], J. D. RYU[2], E. DIAS-FERREIRA[2], G. MAIMON[2];
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Abstract: Studying head-fixed animals allows neuroscientists to make physiological and behavioral measurements at high resolution, but these measurements are typically made for only a few hours per animal. Here we describe an easily clonable experimental system that allows individual head-fixed *Drosophila* to live for up to two weeks, and potentially longer, within a virtual reality environment. The flies walk on an air-supported ball while viewing a panoramic visual environment. They receive hundreds of small sugar drops, at experimentally defined moments, as food. The rigs are compact, such that two dozen can fit in a small room and they are easily adaptable to varied experimental needs. Using these rigs, we show that when *Drosophila* are allowed to freely navigate in a simple virtual environment that consists of a single, distant, visual orienting cue (akin to the sun), individuals maintain a consistent angle in reference to the cue for days to weeks while progressing forward in the virtual world. Each fly walks along a unique, preferred, travel direction for tens to hundreds of meters from her start location. The preferred direction can be considered an active, navigational goal angle because individuals will repeatedly correct for experimentally induced virtual rotations away from this angle. We show that flies rely on the distant visual orienting cue to effectively progress forward along the goal angle—walking in circles without it—and that they return to walking forward along the same goal angle in the morning after spending a full night (twelve hours) without the cue. These data argue for the existence of navigation-related signals and mechanisms in the *Drosophila* brain with a persistence time on the order of days to weeks.

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Poster

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Topic: H.09. Spatial Navigation

Support: Helen Hay Whitney Foundation Postdoctoral Fellowship
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HHMI

Title: Predictions of head direction instruct the learning of a visual-to-head-direction map via axonal biochemistry

Authors: *S. THORNQUIST[1], G. MAIMON[2];
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Abstract: Animals ranging from insects to vertebrates continuously estimate their angular bearing. These estimates are maintained by sensory inputs, but the sensory features that reliably indicate an animal's head direction vary across views within and across environments. How do navigational systems identify informative sensory inputs to guide head-direction estimates? We argue that the *Drosophila* ellipsoid body employs dynamic cAMP signaling in the axon compartments of sensory neurons to infer which visual-sensory signals should influence head-direction estimates. Levels of cAMP rise and fall on seconds-or-faster timescales in a population of visual neurons that are immediately presynaptic to head-direction cells, tracking changes in the orientation of the fly as it navigates in virtual reality. The spatiotemporal dynamics of cAMP suggest that its concentration functions as an *eligibility signal* for incremental plasticity at the synapses between visual neurons and head-direction cells. Specifically, when flies turn, ellipsoid-body cAMP levels are highest at those visual-to-head-direction synapses that are about to become active, *i.e.*, at those synapses where it is most sensible to learn a visual-to-head-direction mapping in the upcoming moment. We show that the activity of the cAMP-sensitive kinase PKA accumulates in a cAMP- and electrical-activity dependent manner in the visual axon terminals. PKA activity acts like a *confidence signal*, tracking the moment-to-moment certainty in whether a given visual synapse should inform the head-direction estimate, and possibly dictate that synapse's strength. Blocking PKA signaling prevents any learned association between the visual world and the fly's internal sense of heading. The emerging picture is that eligibility and confidence calculations are performed within individual axonal compartments using biochemistry--a more energy efficient mechanism of computation than neural-circuit based mechanisms--to make predictions that instruct learning. Including predictions in the acquisition of visual-to-head-direction associations likely improves the efficiency of learning**.** The rapid kinetics of cAMP clearance in the ellipsoid body are well-matched to the computational role of cAMP in this system. In other contexts and neural systems, cAMP levels are much longer-lived. Bespoke cAMP dynamics across systems underscores that quantitative neural computations, particularly slow ones, emerge from a constant interplay between electricity and biochemistry in neural networks.

Disclosures: S. Thornquist: None. **G. Maimon:** None.

Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

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Topic: H.09. Spatial Navigation

Support: NIH 1U01NS126050

Title: Spatial cognitive map formation requires path integration but not distal landmarks

Authors: *R. GRGURICH[1], H. T. BLAIR IV[2];
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Abstract: Rats were trained to perform a 2-start 2-choice (2S2C) task on a plus maze surrounded by a 2x2 m square track (田); automatic doors controlled access to maze segments. A reward (sweet milk) was dispensed at only one corner (e.g., NE; counterbalanced by rat). Rats began each trial facing the maze center from 1 of 2 opposing start arms (e.g., N or S); the path forward into the opposing start arm was blocked by a door, requiring the rat to turn left (L) or right (R) at the 1st choice point, followed by a 2nd L/R choice at a side T-intersection, then arrival at a corner. The optimal path to goal from one start arm was 2 repeated turns (e.g., L-L to reach NE from N) and from the other was 2 alternating turns (e.g., R-L to reach NE from S). After reward consumption, rats were guided to the next start arm for a new trial. There were 3 versions of the task: 1) fixed frame (FF; n=16) where start arms, goal corner, and an extramaze visual landmark remained at fixed locations so inertial and distal cues were concordant, 2) rotating frame (RF; n=13) where start arms, goal corner, and landmark were rigidly rotated by a random multiple of 90° between trials so inertial and distal cues were in conflict, 3) no cue (NC; n=11) where start arms & goal corner remained at fixed locations with no landmark so only inertial cues were available. All 3 versions were acquired in ~160 trials (Kruskal-Wallis p=.22). Rats then received a probe session; the goal location remained fixed in the landmark (FF & RF groups) or room (FF & NC groups) reference frame, but 16/40 trials began from a new start arm (e.g., W from which the optimal path to goal was a novel choice sequence: L-R). FF & NC rats followed the novel path to goal, but NC rats did not (even when probed under FF conditions) indicating failure to form a cognitive map. 24h later, rats were given a reversal session in which trials began from the original 2 start arms, but the goal was moved to the opposite corner (e.g., from NE to SW) reversing the start arms from which the two familiar turn sequences were performed. FF rats acquired reversal in a median 21.5 trials, likely by assigning new values to existing place representations in the cognitive map. NC rats acquired reversal significantly faster (median 12 trials, Wilcoxon p<.0001), likely by rotating their existing cognitive map (since it was unanchored to any conflicting distal cues) when the goal was encountered in its new location. RF rats failed to reverse after 64 trials, but reached criterion in a median 47 trials when reversed under FF conditions, likely by forming a new cognitive map from path integration during early FF trials. These findings imply that rats only form spatial cognitive maps when path integration is available as a navigation strategy.

Disclosures: R. Grgurich: None. **H.T. Blair:** None.

Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

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Topic: H.09. Spatial Navigation

Support: SFB 1372

Title: Neuronal signature of spatial memory in the hippocampus of homing pigeons

Authors: *M. ZIEGLER[1], G. HIDALGO GADEA[1], J. M. TUFF[1], M. INDA[1], R. PUSCH[1], T. OTTO[1], J. M. ROSE[1], O. GUNTURKUN[2], N. ROOK[1];
[1]Ruhr-University Bochum, Bochum, Germany; [2]Fac. of Psychology, Dept. Biopsychology, Ruhr-University Bochum, Bochum, Germany

Abstract: Spatial cognition is a field of research that investigates the basis of human and animal navigation and orientation. Many animals possess excellent spatial abilities like homing and migration that can be found across the animal kingdom. The hippocampus is an essential brain area for memory formation and spatial cognition in both mammals and birds, which has been shown physiologically in the form of place and head-direction cells as well as functionally through for example ablation studies. However, in contrast to mammals, the precise pattern of hippocampal spatial processing is still rather unknown for birds, especially pigeons. To gain deeper insights into the neuronal signature of spatial memory in pigeons, we conducted a spatial discrimination task (experimental group) and a feature-based discrimination task (control group) in a hexagonal area to investigate learning behavior as well as the underlying neuronal activation patterns using immediate early genes. Moreover, we quantified nitric oxide and doublecortin in both groups, which are two other neurochemical markers that have been associated with spatial learning in mammals. Overall, we found task-related differences in the speed of learning the respective tasks furthermore DeepLabCut analysis revealed differences in locomotion strategies. Additionally, we found differences in hippocampal expression profiles of ZENK, NADPH and DCX between the experimental (spatial discrimination) and control (feature-based discrimination) groups but only in specific hippocampal subdivisions. It can thus be concluded that spatial learning is processed in specific subareas of the pigeon hippocampus as well as that it leads to an increase of neuronal recruitment.

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Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

Location: MCP Hall A

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Program #/Poster #: PSTR370.09/W24

Topic: H.09. Spatial Navigation

Title: Evidence of allocentric spatial learning in male rats with large lesions of the hippocampus

Authors: *J. WEBB[1], M. G. REYNOLDS[2], N. M. FOURNIER[2], H. LEHMANN[2];
[1]Psychology, Trent Univ., Peterborough, ON, Canada; [2]Dept. of Psychology, Trent Univ., Peterborough, ON, Canada

Abstract: The hidden platform version of the Morris Water Task (MWT) is widely used to assess spatial learning and memory in rats. In this task, rats must learn and recall the location of a submerged platform within a circular pool. Success in finding the location of hidden platform from any location in the pool requires the integration of various types of information, such as discerning the location of the platform in relation to fixed (allocentric) environmental cues. While lesions of the hippocampus (HPC) typically disrupt this form of allocentric learning, HPC rats show performance improvement over repeated trials by resorting to alternative search strategies based on body-centered (egocentric) cues. In the current study, we investigated whether the size of HPC lesions, which is often associated with amnesic effects, correlates with allocentric impairments in the MWT. Archival data of 53 HPC (lesion sizes between 51% and 96%) and 14 control rats that were all trained using the same MWT protocol (9 acquisition trials) were analyzed for swim performance and strategies. The data showed that both the HPC and control rats showed evidence of learning in the task as supported by a decrease in swim distance to find the platform over trials, but the HPC group continued to show longer swim distances even at the end of training. This deficit was not associated with lesion size. Further analysis revealed that during initial acquisition trials, the control group engaged in random search strategies to find the platform and, by the 5th trial, shifted to a persistent allocentric search strategy to locate the platform. The HPC group similarly displayed a random swim pattern during the initial learning trials, but over 50% of the HPC rats shifted to an egocentric search strategy in the late swim trials. Interestingly, 20% of the HPC rats adopted and maintained an allocentric. Neither allocentric nor egocentric swim search patterns in the lesion group showed any correlation with the extent of HPC damage. These findings suggest that a subgroup of rats with HPC lesions, even nearly complete, can learn and remember spatial allocentric information in the MWT. Our findings highlight the potential role of other brain regions in supporting spatial learning and memory in the absence of the HPC.

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Poster

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Topic: H.08. Learning and Memory

Support: CGS-M NSERC Grant 565525
OGS Scholarship Award
NSERC Discovery Grant 506730
CIHR Grant 507489

Title: Functional characterization of the medial mammillary nuclei in spatial memory

Authors: *K. D. MAR[1], C. SO[2], J. KIM[1];
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Abstract: The mammillary bodies (MB) have been implicated in processing spatial information; however, the role of distinct MB nuclei remains elusive. The organization of inputs and outputs of the medial (MM) and lateral (LM) MB nuclei are parallel to one another and are topographically organized, which may represent a functional differentiation within the structure. To selectively investigate the role of the MM in spatial memory, we coupled behavioral testing across differently cued spatial memory tasks with functional inhibition of the MM and MM projections to the anteromedial thalamic nuclei (AM) using synaptic silencing and optogenetics. The spatial memory tasks employed in our investigation evaluate egocentric and allocentric spatial reference frames, and the resolution of conflict between both reference frames during naturalistic escape on the Barnes maze. To selectively target MM neurons, we procured the Nts-Cre mouse line that selectively expresses Cre in the MM. We began by synaptically silencing the MM soma using Cre-responsive AAV expressing tetanus toxin light chain. At 3-4 weeks post-op, mice displayed profound impairments in visuospatial abilities, including egocentric spatial memory and balance. Attempts to continue testing the mice were unsuccessful at 5 weeks post-op due to progressive visuospatial decline. Next, we used optogenetics to transiently inhibit the MM soma or MM projections to the AM by expressing Cre-responsive ArchT in the MM. Inhibition of MM projections to the AM led to marked impairments in egocentric spatial memory not observed when inhibiting the MM soma. The present results suggest the MM may serve a functional role in the integration of spatial cues necessary for spatial memory and navigation in an environment more broadly.

Disclosures: K.D. Mar: None. **C. So:** None. **J. Kim:** None.

Poster

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Program #/Poster #: PSTR370.11/W26

Topic: H.09. Spatial Navigation

Title: A novel labyrinth test for assessing naturalistic spatial memory and decision-making in humanized knock-in mouse models of Alzheimer's disease

Authors: *P. HONMA[1], S. BANGERA[2], R. THOMAS[2], J. SHIN[2], D. XIA[3], P. SANCHEZ[4], J. J. PALOP[5];
[1]UCSF/Gladstone, San Francisco, CA; [2]Gladstone Inst., San Francisco, CA; [3]Denali Therapeut., South San Francisco, CA; [4]Denali Therapeut., San Francisco, CA; [5]Gladstone Inst. & UCSF, South San Francisco, CA

Abstract: Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by pathological changes, such as extracellular amyloid-beta (Aβ) deposits and microgliosis, neuronal dysfunction, and cognitive decline. Novel humanized *App* knock-in (KI) mouse models recapitulate key AD pathologies and avoid potential artifacts induced by APP overexpression, but have much milder behavioral phenotypes. To address this issue, we have developed a complex labyrinth maze, containing reward and non-reward paths, loops and dead ends, in which mice can freely navigate overnight between their home cage and the maze to obtain sucrose pellet rewards (target zone). We tested this maze in WT and App^{SAA} KI mice, which carry a humanized Aβ region with three FAD mutations (Swedish, Arctic, Austrian). We first demonstrate that both WT and App^{SAA} mice are able to successfully learn the task within one overnight trial, as evidenced by a strong preference for the reward path and target zone. However, App^{SAA} mice showed an impaired ability to navigate to the reward location, as seen by increased time in loops and non-reward paths. To gain further insights into the behavioral states underlying these navigational strategies, we employed discrete-time Hidden Markov Models (HMM) to infer latent behavioral states based on tracking data. Using this method, we uncover a unique behavioral signature at decision-making nodes that is altered in App^{SAA} mice. Taken together, this research provides a novel behavioral paradigm for detecting spatial learning and memory deficits in humanized *App*-KI mice that typically have subtle behavioral phenotypes.

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Poster

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Topic: H.09. Spatial Navigation

Support: NSF Grant 1703340

Title: To trust or not to trust: going the distance in rat-robot social and spatial navigation in megaspace

Authors: *H. L. JENSEN[1], H. C. WITHERSPOON[1], J.-M. FELLOUS[2];
[1]Psychology, Univ. of Arizona, Tucson, AZ; [2]Psychology and Biomed. Engin., Univ. of Arizona, Tucson, AZ

Abstract: Rodent spatial navigation in complex, socially-relevant environments remains understudied. We explored the social behaviors of rats in megaspace, allowing them to experience different types of interactions with controlled robot counterparts. The megaspace is a 18 square meters rectangle that includes 3 starting locations and 54 potential targets. Within megaspace, modular boundaries and objects can be added alongside one robot. Four food-restricted brown Norway rats (2 males) were used. The robot consisted of a joystick-controlled Sphero SPRK+ model equipped with a baited wheeled cart. Experimental tasks were designed to encourage rats to follow the moving robot in pursuit of a food reward.
The control task allowed rats to explore the megaspace and encounter the robot while it was stationary, permitting us to analyze rat navigation strategies as a function of robot movement types, without additional complicating factors in their environment. In the first task, the movement of the rat and robot were simultaneously tracked. Rats displayed unique spatial navigation behaviors in response to three distinct patterns of robot movement—twitch, straight, and curve conditions. In the second task, rats were placed in a complex maze and led by their robot companion to several rewards at various dead-ends. Occasionally, the rats were subjected to deception by being led to a dead-end without a reward. In the first task, changes in robot movement conditions resulted in differences in rats' time spent in physical proximity to the robot, time spent mimicking the robot's movements, and approach velocity. In the second task, we hypothesized that the rats would take longer to find their reward after a deceptive lead from the robot, as well as an increased time to obtain the reward on a trust trial immediately following a mistrust.
Our pilot work revealed that rats were able to successfully navigate in megaspace away from boundaries, and utilized helpful interactions with a robot in order to locate their reward. They also were found to adjust their navigation pattern as a function of specific robot movements. Finally, rats displayed a range of dyadic behaviors and navigational strategies in response to the trustworthy or untrustworthy nature of their interactions with the robot. Our results are the first step in studying the extent to which rats adjust their navigation as a function of social interactions. Next steps include the development of additional paradigms to study the interplay between spatial navigation and social interaction with robots and recordings from hippocampal CA1, CA2 and CA3 areas during these tasks.

Disclosures: H.L. Jensen: None. **H.C. Witherspoon:** None. **J. Fellous:** None.

Poster

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Program #/Poster #: PSTR370.13/W28

Topic: H.09. Spatial Navigation

Title: Single trial analysis of plus-maze decision making suggests differences in cognitive demands based on recent decision history

Authors: *Y. LIU[1,2], M. MIN[1], J. BJORK[1], D. H. HECK[1,2];
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Abstract: Spatial working memory (SWM) is a cognitive skill critical for survival-relevant behaviors. SWM in rodents can be tested by measuring spontaneous alternations during free exploration of a plus maze to evaluate the animals' ability to remember and alternate between different arms of the maze without explicit training. Traditionally, any sequence of 4 arm-entries without repetition is considered a correct spontaneous alternation (CSA). Other sequences outside of CSA are classified as incorrect spontaneous alternations (ISA). In healthy mice around 30-40% of sequences are CSA, with a chance level of approximately 22.2%. A higher percentage of CSA indicates better SWM and cognitive flexibility. In contrast, a decrease in CSA is interpreted as a deficit in SWM. Using the traditional definition of CSA any of the first three arm choices in the CSA may have also occurred during the three choices preceding the CSA, and thus be part of repeat trials (RPs). Focusing on a single trial or choice-by-choice analysis we observed differences in time spent in the center between RPs and non-repeat trials (NRPs), indicating possible differences in cognitive processes. This novel behavioral phenotype may be relevant for understanding central mechanisms of SWM and decision-making processes. Twenty adult mice (C57B6/J; sex-balanced) were tested in Plus-Maze tasks, one test each day, over four consecutive days. Results from the first day were treated as task habituation, and data from days 2 to 4 were analyzed. Exploratory trials in the Plus-Maze were classified as RP, NRP, and ISA. Similar to the evaluation of CSA, the percentage of NRP (47.9±0.9) is higher than that of the estimated chance level (34.8±0.7) (Two-Sample t-test: p=0.0000). Exploratory time spent in the Plus-Maze center area (CNT) varies depending on the trial types. The average CNT for the RPs (3.3±0.1s) is longer than for the NRPs (2.7±0.1s) (Two-Sample t-test: p=0.0051). The CNT for the ISAs (3.2±0.2s), which is similar to the RPs, trends higher than that for the NRPs but is not significant. We speculate that the longer CNTs for the RPs are linked to processing of the memory of previously visited arms. The differences in times spent in the center between RP and NRP trials suggest differential cognitive demands based on recent decision history.

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Poster

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Program #/Poster #: PSTR370.14/W29

Topic: H.09. Spatial Navigation

Title: Mice rapidly learn hierarchical models of complex environments during spontaneous exploration

Authors: T. MA[1], A. M. HERMUNDSTAD[2], ***J. VOIGTS**[2];
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Abstract: In natural settings, animals must navigate richly structured sensory surroundings and rapidly adapt to changes in these surroundings. While many studies have explored navigation in mazes and open arenas, relatively little is known about how animals navigate in naturalistic terrain without clearly defined routes. Here, we probe the structure of mouse behavior in a complex, reconfigurable 3D arena in darkness and without explicit reinforcement. Mice quickly converge on a set of running and jumping paths through the arena. We developed new algorithms to partition this behavior into a set of motifs based on re-occurring path segments; this enabled us to describe long paths as hierarchical compositions of shorter sub-paths. Among the paths taken by the mice, highly compositional paths are lower in entropy, emerge later in time, and traverse more sensory diverse regions of the arena. We then introduced a local perturbation to the arena that interacted with existing composite paths. This led to a rapid emergence of new motifs that elicited non-local changes in behavior. Together, these results provide a lens for studying complex, long-timescale behavior by quantifying its compositional structure.

Disclosures: T. Ma: None. **A.M. Hermundstad:** None. **J. Voigts:** None.

Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.15/W30

Topic: H.09. Spatial Navigation

Title: Chronic functional ultrasound imaging on rats during free exploration show robust link between cerebral blood volume changes and animal speed in the hippocampal formation

Authors: *F. CYBIS PEREIRA[1,2], S. BHATTACHARYA[2], S. PEZET[3,4], M. TANTER[5,4];
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Abstract: Brain-wide functional neuroimaging of freely moving animals are key to understanding how cognitive behaviors may emerge from dynamic activation across different areas of the underlying neural circuitry. Functional Ultrasound (fUS) imaging has recently been demonstrated to robustly record brain-wide cerebral blood volume (CBV) dynamics as an indirect measure of neural activity over several weeks or months in freely moving rodents (Bergel et al. 2018). Here we studied freely moving rats in naturalistic behavior exploring an open arena using fUS. We applied a mass-univariate GLM approach to several spatial navigation parameters (animal position, head direction, speed, proximity to borders, acceleration) and we

show robust CBV changes of the hippocampal formation (dorsal hippocampus, entorhinal cortex, subiculum) correlated with the animal speed, across several sessions and animals. Activation lags between MEC and DG in the order of hundred of milliseconds corroborate recent results in electrophysiology (Kropff et al. 2015). Voxel-wise multivariate approaches allowed us to decode animal speed as well as 74% correlation between true and decoded speeds in a leave-one-session-out cross-validation pattern. ROI-based multivariate approaches showed promising decoded speeds in a leave-one-animal-out pattern. Minute-scale oscillations during spatial navigation (Gonzalo Cogno et al. 2024) could also be found voxel-wise in the same hippocampal regions and seems to also be correlated to low frequency animal speed. Functional Ultrasound imaging emerges as an interesting tool for unconstrained deep brain imaging during spatial navigation in rodents.

Disclosures: F. Cybis Pereira: A. Employment/Salary (full or part-time):; Iconeus. **S. Bhattacharya:** A. Employment/Salary (full or part-time):; Iconeus. **S. Pezet:** None. **M. Tanter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus.

Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.16/W31

Topic: H.09. Spatial Navigation

Support: NIH U19NS118246

Title: Primate Gaze Behavior Reflects Dynamic Decision-Making in Naturalistic Navigation

Authors: *W. CHOI, P. ALEFANTIS, G. ANDREADAKIS, D. E. ANGELAKI;
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Abstract: The adaptive updating of beliefs in response to dynamically changing sensory environments is a key component of effective decision-making. While extensive research has addressed decision-making in static contexts, continuous, closed-loop decision-making where action reciprocally influences visual perception remains less explored. Visual path integration provides the platform to understand continuous decision making with a closed loop between action and perception. We used simultaneous and sequential target presentation during virtual navigation to reveal the mechanisms underlying adaptive decision making under time-varying environments. We hypothesized that primates adjust their gaze to actively integrate the time-varying sensory information to guide future decision making in a naturalistic environment. Monkeys and humans engaged in a visual navigation task, using a joystick to steer toward transiently cued target locations in a three-dimensional virtual reality (VR) environment. Two targets appeared either simultaneously or sequentially, while each target was associated with the same amount of reward. Subjects were free to choose which target to navigate towards. The task

required memory of target location, update of internal beliefs regarding self-position, and cost-effective navigational actions. Analysis of navigational strategies revealed that although both humans and monkeys always preferred proximal and centrally located targets, there was a noticeable propensity to select the most recently-flashed target, revealing that primates dynamically update their beliefs with new sensory information. As shown previously, eye movements are continuously tracking target location, even after the target was no longer visible. During sequential target trials, we found that eye movements prior to the second target introduction could reflect the change-of-decision; Specifically, if the eyes are not following the first target at the timing of the second target presentation, it is more likely to choose the recently introduced target. Using a linear regression model, we show that eye movements are strongly correlated with the position of the target chosen even before the second target appeared, highlighting the role of gaze dynamics in sensory integration and future planning. Our study shows that eye movements reflect the adaptive update of beliefs, emphasizing the role of eye movements during continuous, naturalistic navigation.

Disclosures: W. Choi: None. **P. Alefantis:** None. **G. Andreadakis:** None. **D.E. Angelaki:** None.

Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.17/W32

Topic: H.09. Spatial Navigation

Support: CRC T2 in Neural Circuits of Cognition and Control
NFRF Exploration grant
UBC Four Year Doctoral Fellowship

Title: Examining hippocampal task-relevant representation in rats freely moving in a virtual-reality Dome apparatus with conflicting cue frames

Authors: *W. FANG[1], R. KORNELSEN[1], A. DHIR[1], I. MORGAN[1], M. S. MADHAV[2]; [1]Univ. of British Columbia, Vancouver, BC, Canada; [2]Sch. of Biomed. Engin., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The hippocampal formation is thought to encode the cognitive map, classically defined as a metric Euclidean representation of the spatial location of an animal. Recent studies indicate that hippocampal neurons can additionally represent non-spatial domains informed by cues that are informative of the animal's behavioral task. We investigate hippocampal encoding of task-relevant cues in freely moving rodents using a virtual-reality Dome apparatus. In the Dome, rats run freely on a circular track while being surrounded by projected visual cues and listening to auditory cues. The animal's location relative to the two kinds of cues moves with respect to the stationary lab frame according to different values of visual and auditory gains. For

an animal, the reward zones are defined at specific locations within the auditory or visual frame, and the reward-associated frame is deemed task-relevant. Rats are trained to request rewards through nose-pokes in the reward zones and behavioral data shows that they were able to perform this task with high accuracy with either auditory or visual task-relevant frames. We recorded population activity in hippocampal CA1, and quantified spatial information scores of CA1 place cells in the circular task-relevant and task-irrelevant frames, and a conjunctive toroidal frame. Preliminary data from the task with an auditory task-relevant frame indicates that CA1 neurons have overall higher information scores in the task-relevant frame. We test whether the relative information content across the three reference frames (lab, visual, and auditory) is dependent on their task relevance. We also quantify the topology of the neural representation using geometric deep learning techniques and compare it with the topology of the task.

Disclosures: W. Fang: None. **R. Kornelsen:** None. **A. Dhir:** None. **I. Morgan:** None. **M.S. Madhav:** None.

Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.18/W33

Topic: H.09. Spatial Navigation

Support: CRC T2 in Neural Circuits of Cognition and Control
Djavad Mowafaghian Centre for Brain Health Kickstart
NSERC Discovery Grant

Title: Investigating hippocampal-prefrontal interactions that represent and modulate contextual navigation

Authors: *A. GHARIB MOMBEINI[1], A. W. LESTER[2], R. KORNELSEN[3], M. S. MADHAV[2];
[1]The Univ. of British Columbia, Vancouver, BC, Canada; [2]Sch. of Biomed. Engin., Univ. of British Columbia, Vancouver, BC, Canada; [3]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The Hippocampus (HPC) and the medial Prefrontal Cortex (mPFC) are key regions involved in planning and execution of tasks involving spatial memory. Activities of place cells in the HPC are believed to create a representation of one's surroundings, referred to as cognitive map. mPFC is believed to encode context, and may generalize information across contexts. Our aim is to delve into neural representations in the HPC and mPFC as the contexts, rules, and spatial locations dynamically change. We are interested in the space of neural representation of the task, rule, and context. We designed and prototyped a rodent maze apparatus. It is a 3x3 grid of interconnected octagonal compartments with walls that can go up and down to have dynamically changing configurations. Our task consists of two distinct sounds cues and two different visual cues projected on the walls at the choice points. All requisite information about

the task is provided at the task's outset. At the onset of each trial, one sound cue plays and this determines which visual cue is associated with the correct path, which the rat follows to reach the reward. We will implant trained rats with Silicon probe assemblies targeting HPC and mPFC to wirelessly record neural activities as they perform the task. We will analyze the collected data to study the neural representations of the context, task, and spatial locations in these two regions. We predict that mPFC neurons will maintain consistent distinct representations of the two rules enabling information to be generalized across contexts, and HPC place cells will encode a graph-like representation of the task that enables rule generalization in mPFC.

Disclosures: A. Gharib Mombeini: None. **A.W. Lester:** None. **R. Kornelsen:** None. **M.S. Madhav:** None.

Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.19/W34

Topic: H.09. Spatial Navigation

Support: SBME faculty startup funds
T2 CRC in Neural Circuits of Cognition and Control
CFI – John R. Evans Leaders' Fund
Djawad Mowafaghian Centre for Brain Health Alzheimer's Disease Research Grant
Jack Brown and Family Alzheimer Research Foundation Grant

Title: The Omniroute maze: a novel rodent navigation apparatus that integrates dynamically configurable routes, sensory cues and automated reward delivery

Authors: *A. W. LESTER[1], A. GHARIB MOMBEINI[2], G. KAUR[1], M. S. MADHAV[1]; [1]Sch. of Biomed. Engin., Univ. of British Columbia, Vancouver, BC, Canada; [2]The Univ. of British Columbia, Vancouver, BC, Canada

Abstract: We constructed a novel maze that enables flexible, real-time control over routes and sensory cues, akin to virtual reality (VR) systems but for unconstrained real-world rodent behavior. The maze measures 90 x 90 cm and features 60 movable wall segments that can be programmatically configured to create unique routes within a 3 x 3 grid. Four projectors, arrayed around the maze's perimeter, display distinct visual cues on both sides of any subset of raised walls and the maze floor. These projectors also house speakers to provide directional auditory cues. The system incorporates high-speed 3D tracking of a rat's position and orientation, allowing for closed-loop control of the paths and environmental cues based on real-time behavior. An automated gantry system delivers food-based rewards anywhere in the maze. Both the hardware components and the electrophysiological data collection system are controlled using the Robot Operating System (ROS) framework. The Omniroute maze supports the

replication of classic behavioral mazes and a variety of configurations to test hypotheses about the interaction between routes, cues, neural representations, and navigational decisions. Its automated reconfiguration, tracking, and reward delivery enable high-throughput experiments on complex navigation behaviors without the potential biases introduced by direct experimenter intervention. Designed from the ground up for robust operation, the Omniroute system utilizes affordable hardware and software to facilitate easy fabrication and assembly ass well as replicability by other researchers.

Disclosures: A.W. Lester: None. **A. Gharib Mombeini:** None. **G. Kaur:** None. **M.S. Madhav:** None.

Poster

PSTR370: Animal Navigation: Maps, Paths, and Circuit Dynamics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR370.20/W35

Topic: E.04. Voluntary Movements

Support: BBSRC BB/V00817X/1

Title: A novel modular maze for behavioral analysis in freely exploring mice

Authors: *M. MARAVALL[1], A. CARRIERO[1], O. JESUSANMI[1], I. MARANHAO[1], S. AL BALUSHI[2], Y. ELIAS RODRIGUES[2], M. BURNELL-SPECTOR[2], M. NOWAK[2], E. WOODS[1], M. I. ELEY[2], A. M. CHAGAS[1];
[1]Sussex Neurosci., Univ. of Sussex, Brighton, United Kingdom; [2]Life Sci., Univ. of Sussex, Brighton, United Kingdom

Abstract: Animals in nature sense their surroundings by actively engaging with them and process the resulting signals according to their utility. Here we developed an experimental architecture for interrogating such capacities in rodents. To allow us to explore context-dependent decision-making, flexible planning and abstraction of sequential rules, the setup needed to provide high levels of experimental control while enabling simple and flexible behavioral task design. Other aims were for the platform to be easy to modify and share and to use inexpensive and readily available components.
Our resulting architecture is based on a modular labyrinth assembled with ‘Makerbeam XL’ posts and PVC/acrylic plastic panels. Following (Rosenberg et al, 2021) the panels are opaque under visible illumination but transparent when illuminated with infrared light. This encourages exploration, as mice experience the labyrinth as a warren of snug, dark corridors, while enabling tracking with any common machine vision method (e.g. Deeplabcut; Mathis et al, 2018). Panels slot into the ‘Makerbeam XL’ posts. To allow flexible reconfiguration of the maze and the creation of arbitrary associations between stimuli, locations and rewards, standard panels at any location can be replaced by mechanical devices for reward dispensing or stimulus delivery (e.g. textures, moveable gratings, 3D-printed shapes). As examples, we provide a food pellet

dispenser and an oriented tactile grating which rotates over 360°: both are 3D-printed and controlled by cheap servo motors activated by microcontrollers. Device motion is triggered when the animal enters experimenter-defined regions of interest in the maze. In our applications, this is achieved through video tracking implemented via OpenCV libraries and a state machine written in Python, but the system can be easily altered. An animal can encounter multiple stimuli as it moves from the labyrinth's origin to any endpoint, permitting the experimenter to set up complex rules or conditions governing whether the mouse will be rewarded, involving e.g. chains or sequences of stimuli. The labyrinth entrance connects to a home or transfer cage, allowing animals to shuttle between cage and maze whenever they choose. Mice readily habituate to this modular maze, are highly motivated to explore it, and display object-in-place recognition during exploration, with no need for fluid or food restriction. We provide examples of behavioral tasks in which mice interact with tactile and auditory stimuli as they move through the maze. Our maze offers a practical and cost-effective approach for studying a wide range of cognitive behaviors in laboratory settings.

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Poster

PSTR371: Learning and Memory in Aging

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.01/W36

Topic: H.12. Aging and Development

Support: NIH AG066901-01A1

Title: Age-related declines in occipito-temporal and occipito-frontal white matter tracts constrain functional networks and disrupt perceptual memory

Authors: *K. D. GILLETTE[1], C. M. HOWARD[2], R. E. CABEZA[3], S. W. DAVIS[4]; [1]Ctr. for Cognitive Neurosci., Duke Univ., Durham, NC; [2]Ctr. for Cognitive Neurosci., Ctr. For Cognitive Neurosci., Duke Univ., Durham, NC; [3]Duke Univ., Durham, NC; [4]Duke Univ. Med. Ctr., Durham, NC

Abstract: With age, our ability to remember perceptual details decreases more relative to conceptual details. Declines in structural connectivity and changes in functional connectivity lead to unexplained questions: Does functional reorganization rely on underlying structure? Do age-related increases in structure-function correlations happen in regions showing the strongest structural decline? Does this structure-function convergence in older adults capitalize on existing structural pathways to aid performance, or is this pattern driven by a reduction in the diversity of connections with negative impacts on behavior? Structure-function interactions tend to be explored in terms of function, which changes with task condition, rather than starting with the

underlying white matter anatomy, which does not change over a typical MRI session. Further, examining structure-function relationships in canonical fiber systems that mediate visual cognition may reveal the primary drivers of age-related declines in perceptual memory. To explore this interaction and its impact on perceptual memory in older adults, we recruited younger (n=26, 16 women) and older adults (n=23, 16 women) to complete an fMRI memory study. On the first day, participants completed a baseline object recognition task. Later, they completed conceptual and perceptual recognition tasks and received a multiband, multiplexed sensitivity-encoding (MUSE) diffusion scan. We then investigated the age-related convergence between structural connectivity (fractional anisotropy values) and functional connectivity during the baseline task. In line with previous literature, we found aging correlates with declines in perceptual memory, widespread declines in structural connectivity, and decreased system segregation of functional networks. Intriguingly, structural connectivity constrained functional connectivity in canonical tracts connecting occipito-temporal and occipito-frontal cortices (UF (uncinate fasciculus): $t = -2.9$, $p < 0.01$; ILF (inferior longitudinal fasciculus): $t = -4.2$, $p < 0.01$), tracts thought to convey perceptual information forward via the ventral stream. We also observed age effects in this structure-function convergence in the anterior thalamic radiation and the corticospinal tract. In a subset of these tracts, the extent of this structural constraint is *negatively* associated with perceptual corrected recognition in older adults (IFOF: $r = -0.49$, $p < 0.02$; UF: $r = -0.43$, $p < 0.05$), but not younger adults. These findings suggest that structural decline in behaviorally-relevant canonical tracts drives functional desegregation.

Disclosures: K.D. Gillette: None. **C.M. Howard:** None. **R.E. Cabeza:** None. **S.W. Davis:** None.

Poster

PSTR371: Learning and Memory in Aging

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.02/W37

Topic: H.12. Aging and Development

Title: Cognitive aging and cerebellum: a fMRI study of the older adults

Authors: *Y. LIN[1], C.-P. LIN[2], L.-H. CHANG[2];
[1]Natl. Yang Ming Chiao Tung Univ., Beitou Dist., Taiwan; [2]Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: Cognitive aging research has traditionally focused on the cerebral cortex, with limited investigation into the role of the cerebellum. However, accumulating evidence indicates cerebellar involvement in various cognitive processes, with different regions associated with distinct functions. Given the decline in cognitive abilities with aging, this study aimed to examine age-related differences in cerebellar activation across multiple cognitive domains. We hypothesized increased cerebellar recruitment in older adults compared to younger individuals to support declining cognitive function.

Using task-based functional magnetic resonance imaging (fMRI), we observed blood oxygen level-dependent (BOLD) activations in the cerebellum of two age groups (older adults: mean age 69.4 ± 2.07 years, n=4; young adults: mean age 21.86 ± 2.04 years, n=7) while performing motor (finger tapping), language (verbal generation), working memory (N-back), and visuospatial (Useful Field of View; UFOV) tasks.

During the motor task, younger adults exhibited increased BOLD signals in the bilateral anterior cerebellar lobes compared to older adults. Conversely, for working memory and language tasks, older adults demonstrated greater activation in the bilateral posterior cerebellar lobes relative to younger individuals. No significant between-group differences were observed for the UFOV task.(Figure)

These preliminary findings suggest distinct cerebellar activation patterns across multiple cognitive domains in older adults. Specifically, increased recruitment of the posterior cerebellum may compensate for age-related declines in cognitive functioning, particularly for working memory and language processes. Overall, our results highlight the potential role of the cerebellum in supporting cognition during aging.

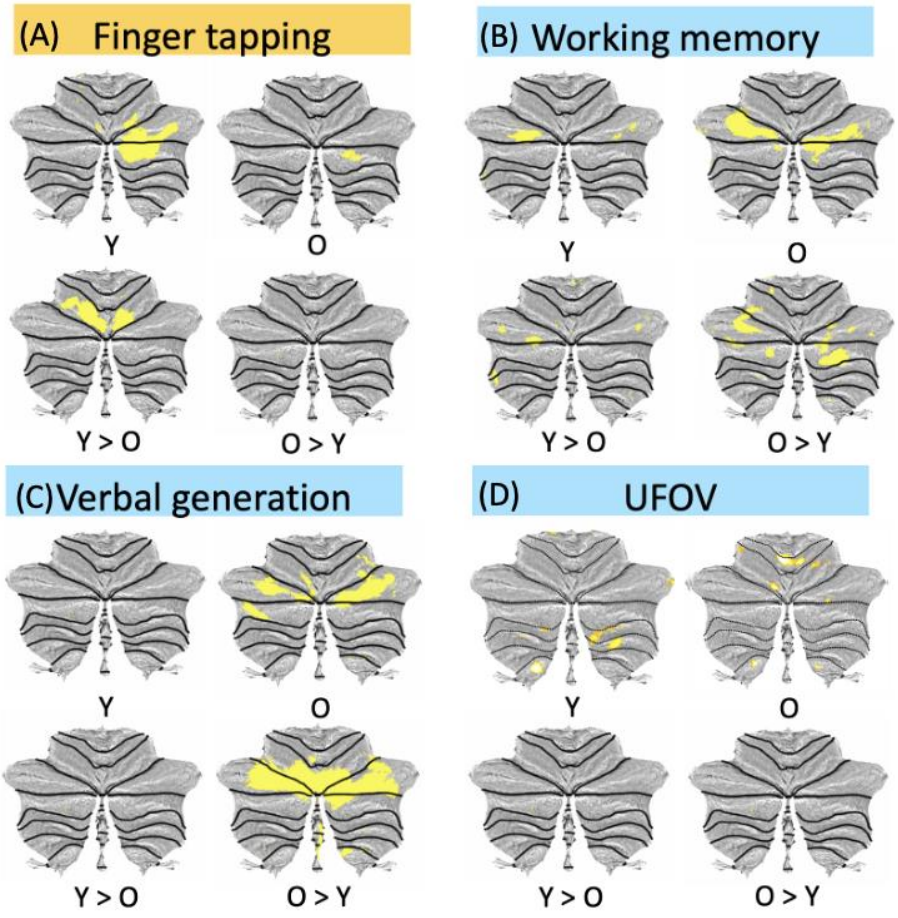

Figure . The BOLD signals of the cerebellum between the older and the younger across multiple tasks.

The BOLD signals in (A) Finger tapping task, (B) Working memory task, (C) Verbal generation task, (D) UFOV task.

Disclosures: Y. Lin: None. **C. Lin:** None. **L. Chang:** None.

Poster

PSTR371: Learning and Memory in Aging

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.03/W38

Topic: H.12. Aging and Development

Title: Call me by your name: the nature of involuntary memory in people with dementia.

Authors: *A. ONZO[1], K. MOGI[2,3], S. HOTTA[4,5];
[1]The Univ. of Tokyo, Meguro-Ku, Tokyo, Japan; [2]Sony Computer Sci. Labs., Shinagawa-Ku, Japan; [3]The University of Tokyo, Megura-Ku, Tokyo, Japan; [4]Keio Univ., Koto-ku/Tokyo, Japan; [5]Designing for Dementia Hub, Tokyo, Japan

Abstract: One of the fears the family members and friends of people with dementia (especially Alzheimer's disease) have is that they will one day be forgotten. In fact, they may be called by the wrong name. But does that really mean that the person with dementia has forgotten the person? It is known that in older people and people with dementia, recent events become harder to remember and old memories become clearer, which is sometimes called a reminiscence bump (Berntsen & Rubin, 2002). When people with dementia see a small child on the street, they may unintentionally recall when their daughter or son was small and call their own child's name to the stranger. Conversely, if they see their own child as an adult and have strong memories of the past, they may not recognize them at that moment and may respond, "Who are you?", giving the impression that they have been forgotten. However, involuntary memories are known to be associative and triggered by a cue, and unlike voluntary memories, in which we make an effort to remember, they are often recalled when there are similarities between the recalled content and the present situation (Berntsen, 2010). If a person mistakes his daughter's name for his sister's name, it may be because they have something in common, such as being a woman or a loved one for him to look after. By looking for commonalities in the mistakes people with dementia made, their family and friends may be able to find hope that, although the name was not recalled successfully, the person with dementia may still consider them as an important person. We observed the misnaming of people with dementia in several residential and daycare facilities in Japan for three months in search of commonalities. The staff in those facilities were asked to fill in a form on the same day when misnaming occurred. They were asked about the situation in which the misnaming occurred (e.g. “Was it a tense or relaxed situation?”), the nature of relationships between those mistakenly called, those whose name was called, and the person with dementia (e.g. “Are they relatives?”), and the personal and affective significance of people for the current life of the person with dementia. The frequency of misnaming depending on the progression of dementia was also analyzed. We found that there were multiple types of involuntary recall, suggesting that even with advanced dementia, people are not living only in the present moment, but are connected to the past, while maintaining emotional memories, such as their love for family and friends. We will discuss the brain mechanisms of each type of involuntary recall.

Disclosures: A. Onzo: None. **K. Mogi:** None. **S. Hotta:** None.

Poster

PSTR371: Learning and Memory in Aging

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.04/X1

Topic: H.12. Aging and Development

Support: R01AG062503

Title: Script generation as a measure of functional decline in older adults with cognitive impairment

Authors: *M. ROSAHL, M. KAPLAN, R. CHATURVEDI, M. MCKNIFF, A. CALLAHAN, G. VALLECORSA, S. HOLMQVIST, D. MCCOURT, T. GIOVANNETTI;
Temple Univ., Philadelphia, PA

Abstract: Subtle changes in naturalistic language have been associated with cognitive abilities in older adults. This study explored script generation as a measure of cognitive and functional decline through healthy cognition, mild cognitive impairment (MCI) and mild dementia. Differences in human-coded analysis of scripts were examined between MCI, mild dementia, and healthy groups. 83 older adults aged 65+ (n=51 healthy cognition, n=23 MCI, n=9 mild dementia) completed a script generation task (SGT) requiring descriptions of the following: making toast, coffee, a sandwich, and lunch. Scripts were scored for total time, number of words, essential and non-essential steps, errors, and commentary words. Participants also performed the Naturalistic Action Task (NAT), which required making meals with real objects. NAT performance was scored for total time, accomplishment steps, and errors. Finally, participants (or their care partners) completed a questionnaire rating their everyday functional abilities (Functional Activity Questionnaire; FAQ). One-way ANOVAs o compared MCI vs. mild dementia vs. healthy groups on the SGT. Spearman correlations examined relations between the SGT and the NAT. On the SGT the number of essential steps (Kruskal Wallis $\chi^2 = 16.76$, df=2, $p < 0.001$) and non-essential steps (Kruskal Wallis $\chi^2 = 7.63$, df=2, $p<0.05$) differed significantly across the groups, such that healthy participants generated more essential steps than the MCI group (Kruskal Wallis χ^2 7.19, df=1, $p<0.01$) and the MCI group generated more essential steps than the mild dementia group (Kruskal Wallis χ^2 =4.99, df=1, $p<0.05$). SGT performance was significantly associated with NAT performance, such that more essential steps ($r=0.45$, $p<0.001$), non-essential steps ($r=0.42$, $p<0.001$), time ($r=0.39$, $p<0.001$), and total words ($r=0.5$, $p<0.001$) correlated significantly with more NAT accomplishment steps. More SGT essential steps ($r=-0.32$, $p<0.01$), non-essential steps ($r=-0.34$, $p<0.01$), and words ($r=-0.26$, $p<0.01$) also were significantly correlated with fewer NAT errors. SGT essential steps were significantly associated with FAQ scores ($r=-0.29$, $p=0.008$). Script generation scores significantly differentiated participants with MCI, mild dementia, and healthy cognition. Script performance was associated with the performance of everyday tasks with real objects and survey measures of everyday

functioning. Script generation tasks provide an accessible, inexpensive measure of cognitive/functional decline and should be considered as a cognitive screening tool for older adults.

Disclosures: M. Rosahl: None. **M. Kaplan:** None. **R. Chaturvedi:** None. **M. Mckniff:** None. **A. Callahan:** None. **G. Vallecorsa:** None. **S. Holmqvist:** None. **D. McCourt:** None. **T. Giovannetti:** None.

Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.05/X2

Topic: H.12. Aging and Development

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Title: Using novelty and expectation violation to characterise the neural underpinnings of superior memory in Superagers

Authors: *M. GARCIA HUESCAR[1,2], B. A. STRANGE[1], D. FRANK[1];
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Abstract: Novelty and expectation violation promote the formation of long-term memory, supported by engagement of medial temporal lobe (MTL) and midbrain structures. These regions also deteriorate during ageing, potentially contributing to an age-related decline in memory performance. Superagers are people aged 80 or older with episodic memory performance as good as healthy people 20-30 years younger, sustained by increased grey matter density in the MTL. Here, we used a task combining novelty and expectation violation together with fMRI to examine neural markers that contribute to the superior memory functions of superagers compared with healthy older adults. Our sample included 21 superagers (mean age=82.9, 12 female) and 20 matched controls (mean age=83.5, 13 female) from the Vallecas Project cohort (Madrid, Spain). Participants were first familiarised with object images and then performed a rule-learning task, associating a cue with a subsequent item (old or new object). During the encoding phase, inside a 3T MRI scanner, they were presented with the same cues preceding familiar and novel objects. Notably, on 30% of the trials, there was a mismatch between the cue and the subsequent object (e.g. novel cue presented before a familiar object). After the scan, a

recognition test was performed, including objects novel at encoding and previously unseen foils. Behaviourally, superagers showed overall superior performance and faster responses compared to controls on the recognition task, although unexpected objects were better recognised than expected ones in both groups. Superagers showed increased activation in the parietal lobe, compared to controls, in response to unexpected objects at encoding, whereas controls showed higher activation in frontal areas when processing novel objects. Future analysis will explore the different contributions of these areas to memory formation as well as the disparities between groups. These results contribute to our understanding of the functional neural underpinnings of superior performance abilities in older age.

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Poster

PSTR371: Learning and Memory in Aging

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.06/X3

Topic: H.12. Aging and Development

Support: PAPIIT-UNAM #IN217221
PAPIIT-UNAM #IN202822
CONACYT #1083933

Title: Healthy aging: factors that protect against cognitive decline

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Abstract: There are age-dependent functional and behavioral changes in cognitive functions such as attention and working memory. Attention filters out irrelevant stimuli and focuses on what is important. This cognitive process relies on two mechanisms: enhancement, which helps to select relevant information; and suppression, which prevents irrelevant information from interfering. When either of these mechanisms fails during information processing, it can negatively impact working memory efficiency (WME). Several protective factors, that prevent or delay age-associated cognitive changes, have a positive impact on attention and working memory. This study aimed to detect factors that might buffer the effect of age on attentional mechanisms (through the duration of eye movements and the amplification and suppression index) and WME (measured by the inverse efficiency index). One hundred and ninety-four

healthy volunteers responded to an experimental task with three conditions, where scenes and faces were presented simultaneously during the encoding phase, and participants were asked during the probe phase: 1. Attend faces/ignore scenes; 2. Attend scenes/ignore faces; and 3. Passive viewing condition (where participants only gazed at the pictures and were requested to indicate the direction of an arrow during the probe phase). Further, they completed questionnaires inquiring about their cognitive reserve, anxiety, and depression (trait and state). The results revealed that the cognitive reserve and sleep duration positively moderate the impact of age on the suppression process. As for the sleep duration, it positively influences WME, while state depression negatively influences it. Similarly, anxiety levels modulate the suppression mechanism on WME; higher levels of anxiety were associated with lower WME as suppression increased. The sleep duration had a differential effect depending on the age group of the participants: as the suppression of irrelevant stimuli increased, lower sleep hours impaired WME only in older adults; but as the suppression of irrelevant stimuli increased, higher sleep hours negatively affected WME in young and medium-aged adults. These findings suggest that cognitive reserve and sleep duration may protect against age-related deterioration, whereas high levels of anxiety and state depression could exacerbate the risk of decline.

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Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.08/X5

Topic: H.12. Aging and Development

Support: 2R01NS107357-6A1

Title: Differential theta modulation of age-invariant and age-related subsequent memory in medial parietal regions

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Abstract: Models of episodic memory drawn primarily from noninvasive data implicate the medial parietal cortex (MPC), including the posterior cingulate cortex and precuneus, in episodic memory processing networks. Moreover, aging research models have characterized these structures as changing in functional organization across the lifespan, correlating age related deficits in automatic-binding processes, or alternative theories such as hyper-binding which leading to extra-encoding errors, or false alarms. Disambiguation of the precise contributions of these regions requires spatially precise data which can be best measured with intracranial

recordings. Such data can also unravel the specific neurophysiological mechanisms that support episodic processing in these areas as part of hippocampal networks. Theta oscillations, which support processes such as inter-regional coordination, represent a key mechanism previously identified in medial parietal recordings in humans. These questions are further highlighted by age-related differences in episodic processing identified in the MPC. We utilized an intracranial recording dataset from 68 subjects to examine neurophysiological signatures of successful encoding memory as participants performed verbal associative recognition. Our data identified age-invariant theta oscillatory dynamics in the bilateral posterior cingulate cortex linked with subsequent recollection and familiarity-based processing. Further, using mixed effects modeling, we demonstrate age-related differences in these oscillatory patterns, especially in the left posterior cingulate and left precuneus, which exhibited an increase in relative theta power of familiar items relative to those items subsequently recollected. We interpret these data within general models of episodic processing, such as the posterior medial/anterior temporal framework, as well as models age-related differences such as the associative deficit hypothesis. Our findings represent one of the first examinations of neurophysiological processes differentiating regions within the MPC linked with age-related changes.

Disclosures: J.L.S. Kriegel: None. **B.C. Lega:** None.

Poster

PSTR371: Learning and Memory in Aging

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NIH – U19NS107609 (E.A.B)

Title: Normative aging and hippocampal lesions differentially impact viewing behaviors in monkeys

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Abstract: Neurobiological changes in the aging hippocampus are thought to underlie age-related changes in memory and cognition, but our current understanding of the relationship between

hippocampal damage and normative aging is limited. Studies in humans and monkeys have shown that saccadic eye movements during the viewing of natural scenes provide a sensitive measure of recognition memory, and that changes in hippocampal activity correlate with memory-related changes in eye movements. However, it is unclear the extent to which viewing behaviors are affected by normative aging and hippocampal damage. Here, we examined viewing behavior in a group of young adult monkeys (avg. age 7.3 ± 1.8 years), before and after bilateral hippocampal lesions, and in a group of aged monkeys (avg. age 21.9 ± 1.8 years). For the young adult group, ibotenic acid was used to create bilateral lesions targeting the hippocampus while sparing surrounding structures and fibers of passage. During the behavioral testing sessions, all groups were presented with full-screen natural images for a cumulative viewing time of 5-7 seconds per image. Blocks of 12-16 novel images were presented, followed by a repeat presentation of the same images. Across a behavioral session, a total of 60-96 unique images (5-6 blocks) were shown, and new images were used for each session. No reward was provided during the image presentation; monkeys were able to earn reward (food slurry) for performance on interleaved eye calibration trials. Our results show that, for all groups of monkeys, visual exploration was greater for novel images compared to repeated images, as indicated by higher saccade rate, lower saccade amplitude, and shorter fixation durations (pairwise Mann Whitney U, Bonferroni corrected, all ps<0.001). However, we identified group differences related to overall viewing behavior. Aged monkeys showed longer fixation durations and explored a smaller percentage of the image than young adult monkeys (pairwise Mann Whitney U, Bonferroni corrected, all ps<0.001). Interestingly, an opposite effect was observed post-hippocampal lesions in the young adult monkeys. Compared to pre-lesion behavior, this group showed a decrease in fixation durations, along with an increase in the amplitude and frequency of saccadic eye movements (pairwise Mann Whitney U, Bonferroni corrected, all ps<0.001). Taken together, these data provide evidence for age-related changes in viewing behavior that differ from changes due to hippocampal lesions. These findings provide compelling motivation for future neurophysiological investigations to advance our understanding of the mechanisms of age-related changes in viewing behavior.

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Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.10/X7

Topic: B.07. Network Interactions

Support: ONR grant N00014-24-1-2014
NINDS training grant NS04554

Title: Age-related deficits in hippocampal throughput and episodic processing are associated with perturbations in GABAergic transmission

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Abstract: Aging is associated with a range of memory impairments with the ability to assemble daily life experiences (e.g. a walk through the park) into narrative episodes being particularly vulnerable. The hippocampus is critical for assembling and retrieving episodic memories and there has been intense interest in determining how its diverse neurobiological operations contribute to these functions. Here we report that episodic memory (i.e., encoding "what" and "when' information) is impaired in early middle aged (12-14mo) male mice and this is associated with striking disturbances in hippocampal network function. Using a novel hippocampal slice preparation that enables recording of CA1 spike output following activation of lateral perforant path (LPP) input, we assessed if and how frequency-dependent signal transformations occurring across the entire hippocampal circuit are altered during early aging. LPP activation engages the "direct" (LPP-CA3-CA1) and "indirect" (LPP-DG-CA3-CA1) sub-circuits in a spatially and temporally distinct manner; our prior work found that the indirect path is particularly critical for driving CA1 spike output. Results indicate that signal throughput in response to LPP stimulation, single-pulses or short trains at theta frequency (10 pulses at 5Hz), is impaired during early-aging. This suggests a defect in indirect path function. A more detailed circuit analysis revealed a decrease in LPP-evoked CA3 spike output, suggesting the ability to engage the dense recurrent CA3 commissural-associational system is reduced during early-aging. This decrease in CA3 spiking is accompanied by a reduction in synaptic levels of the α2 $GABA_AR$ subunit within CA3 stratum radiatum suggesting GABAergic transmission is altered. Indeed, the filtering of inputs arriving at beta frequencies and above (i.e., >20Hz), an operation dependent upon recruitment of inhibitory GABAergic transmission in CA3, is significantly reduced by 12-14 mo.Ongoing studies aim to test if the age-related decrease in $GABA_AR$ subunit expression is specific to α2, and if such changes occur only at synapses in CA3 stratum radiatum. We propose alterations in inhibition in field CA3 influences the integration of the spatio-temporally distinct signals conveyed via the direct and indirect LPP inputs to this subfield such that the probability of the indirect sub-circuit initiating CA3 pyramidal cell spiking is reduced. Such perturbations in inhibitory transmission within the hippocampal circuit, evident early in the aging process, have pronounced effects upon signal throughput critical for episodic processing.

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Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.11/X8

Topic: H.12. Aging and Development

Support: Intramural Research Program of the NIH, National Institute on Aging

Title: Neurobiological Effects of Antiepileptic Drugs in Rats with Age-related Spatial Memory Deficits

Authors: *D. RAMEZAN[1], C. MYRUM[1], Z. UTTKE[2], P. R. RAPP[2], E. PEREZ[2];
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Abstract: Electroencephalogram (EEG) recordings in rats and mice commonly display prominent 7-12 Hz oscillations known as sharp-wave discharges (SWDs) that are usually brief (1-2 s), terminate abruptly, most often occur along with vibrissa twitching during quiet wake, and increase in duration and number with age. Elevated neural activity within specific circuits of the hippocampal memory system has emerged as a prominent signature of poor cognitive outcome in aging, though it is unknown whether SWDs might contribute to hippocampal hyperactivity and associated spatial learning capacity in rodent models of normal cognitive aging. Pharmacological approaches to reducing excessive hippocampal activity, and thus restoring cognitive function in aged rats, has included administration of the antiepileptic drug levetiracetam (LEV). Here, we first examined whether SWDs are associated with cognitive outcome in a well-characterized rodent model of normal cognitive aging, Long-Evans (LE) rats. Spatial learning capacity was assessed using the Morris water maze, and aged rats that performed on par with young (Y) were categorized as aged unimpaired (AU) while those that performed worse were considered aged impaired (AI). We collected electroencephalogram (EEG) data of all Y, AU, and AI animals for 24 h and quantified SWD occurrence/duration. We found that SWDs were not associated with cognitive outcome ($p>0.05$), but aged rats (AU+AI), compared to Y, had significantly more SWDs ($p=0.037$). Time spent in SWDs did not differ for Y/AU/AI comparisons, nor a Y/AU+AI comparison (p's>0.05). These data indicate that SWDs are unlikely to account for cognitive deficits observed in aged rats with memory impairment. Next, we carried out a within-subject pharmacological approach, testing the efficacy of LEV at reducing SWD activity among aged AI rats, in comparison to another antiepileptic drug, ethosuximide (ETX), which unlike LEV, appears not to hold cognitive therapeutic potential. Three doses of each drug of each drug were administered in an ascending/descending order: 1.25, 10, and 50 mg/kg LEV; 25, 100, 200 mg/kg ETX; or saline control. EEGs were recorded for 3 h following each injection, and SWDs were quantified. While LEV did not significantly reduce the number ($p>0.05$) or duration ($p>0.05$) of SWDs, ETX significantly reduced both the number ($p<0.0001$) or duration ($p<0.0001$) of SWDs. Given that these doses of LEV are within the range shown to be effective at improving cognition in AI rats, but were ineffective at reducing SWDs, further indicates that SWDs are not coupled to cognitive capacity among aged LE rats.

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Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.12/X9

Topic: H.12. Aging and Development

Support: MRC DTP RE18102

Title: Exploring the role of H3K4me3 in age-related cognitive decline

Authors: *S. U. BHATT[1], L. PÉREZ-SISQUÉS[2], A. GRAHAM[1], H. KALPAGE[3], R. GERKMAN[4], D. P. MATHEOS[5], P. SMETHURST[6], M. A. WOOD[7], S. GILLOTIN[8], K. P. GIESE[9], M. BASSON[10];
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Abstract: Age-related cognitive decline is characterized by impairments in memory and learning and is becoming a prevalent problem as societies shift towards an aging demographic. Learning and memory are associated with the reversible induction of specific histone post-translational modifications (PTMs) like histone 4 lysine 12 acetylation (H4K12ac) and histone 3 lysine 4 trimethylation (H3K4me3). Both H4K12ac and H3K4me3 are typically found at active gene promoters. H4K12ac induction is blunted in the hippocampus of aged mice, and restoration of its levels by administration of deacetylase inhibitors has been shown to reduce cognitive deficits. However, it remains to be seen if other histone PTMs permissive for transcriptional induction, like H3K4me3, are affected during learning in the aged hippocampus. Aged C57BL/6J male mice have been shown to have deficits in hippocampus-dependent learning and memory tasks, as well as memory reconsolidation. We confirmed that aged (18 and 24 month old) female mice are also deficient in hippocampus dependent learning in the object location memory (OLM) test. These mice also showed deficits in memory updating, both in the objects in updated locations (OUL) task and contextual fear conditioning (CFC) test followed by administration of the protein synthesis inhibitor anisomycin to disrupt memory reconsolidation. To explore changes in H3K4me3 levels, Western blots, qPCRs, and immunostainings were used to compare histone modifications in the hippocampus between 3-month-old and 24-month-old mice at various time-points after CFC. While young mice showed an induction in H4K12ac and H3K4me3 three hours post-CFC, this induction was deficient in aged female mice. Intriguingly, both H4K12ac and H3K4me3 levels were elevated in aged mice at baseline, without CFC induction. Administration of WDR5-0103, a potent inhibitor of the methyltransferase machinery responsible for H3K4me3, could restore normal H3K4me3 levels and rescue of learning in the object location memory task. Using the immortalized hippocampal cell line, HT22, immunocytochemistry-based high throughput screens for potential compounds that can restore H3K4me3 levels are being conducted. Together, this project will elucidate the contribution of inducible histone PTMs to age-related cognitive decline and, in the long term, facilitate the

discovery of selective, specific, and effective compounds to restore normal PTM levels and thereby reverse cognitive deficits.

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Poster

PSTR371: Learning and Memory in Aging

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Topic: H.12. Aging and Development

Support: NIH R01NS102448
VA I01BX003195
PHS K12 GM111726

Title: Targeted deletion of kynurenine 3-monooxygenase preserves non-associative and associative learning and memory during aging in mice

Authors: *M. DE LA FLOR[1], M. BUCKNOR[2], N. KUHN-SANDOVAL[3], B. MOORE[3], S. HARRISON[2], D. LOZANO[4], J. C. O'CONNOR[3], E. KOKOVAY[2];
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Abstract: Chronic age-related inflammation has been linked to progressive declines in learning and memory. Oxidative kynurenine pathway (KP) metabolism is increased by pro-inflammatory cytokines and leads to elevated levels of neurotoxic metabolites such as quinolinic acid (QA). These metabolites may contribute to impairments in learning and memory during aging. Studies demonstrate that inhibition of kynurenine 3-monooxygenase (KMO), the rate-limiting enzyme for oxidative kynurenine metabolism, reduces QA while increasing kynurenic acid, a neuroprotective metabolite. Our research demonstrates that genetic deletion of KMO promotes neurogenesis and cell proliferation in the subventricular zone and hippocampal subgranular in adult mice in vivo. We hypothesized that KMO deletion may confer neuroprotection as mice age. To test this, we evaluated both non-associative and associative learning and memory in young, middle-aged, and old male and female $KMO^{-/-}$ mice and age-matched wild type (WT) controls. To assess non-associative learning and memory, we employed the olfactory habituation/dishabituation test. Young WT and $KMO^{-/-}$ mice displayed similar levels of habituation and dishabituation to odors. However, middle-aged and old WT mice showed

significant impairments in their ability to habituate and dishabituate to odors. In contrast, middle-aged and old $KMO^{-/-}$ mice maintained their ability to habituate and dishabituate to odors. To evaluate associative (spatial) learning and memory, we employed the Barnes Maze test. Our analysis revealed no differences in latency, speed, or distance to locate the escape box (EB) between young and middle-aged WT and $KMO^{-/-}$ mice. However, old $KMO^{-/-}$ mice significantly outperformed old WT mice in these measures. Remarkably, old $KMO^{-/-}$ mice exhibited a greater tendency to employ hippocampal-dependent search strategies in the Barnes maze to locate the EB compared to old WT. Taken together, these findings establish that reduction of neurotoxic metabolites, downstream of KMO, preserves learning and memory in aged and old $KMO^{-/-}$ mice, suggesting a potential mechanism underlying cognitive impairments in aging.

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Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.14/X11

Topic: H.12. Aging and Development

Support: NIH Grant P01AG009973

Title: Upregulation of neuronal pentraxin 2 to boost circuit inhibition improves memory performance of cognitively impaired aged rats

Authors: J. ATUFA[1], A. BECKER[1], J. ZHOU[2], P. WORLEY[2], M. GALLAGHER[1], A. BRANCH[1], *M. KOH[1];
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Abstract: Aberrant excess neural activity in the hippocampus contributes to memory impairment in aged humans and animals. The overactivity has been shown in a rodent model of aging to be driven in significant part by reduced feedforward synaptic inhibition in the input of lateral entorhinal cortex (LEC) onto granule cells in the dentate gyrus (DG) of the hippocampus (Tran et al., 2019). One potential mechanism to that reduced inhibition is a decreased recruitment of DG parvalbumin inhibitory interneurons by LEC inputs. As a strategy to improve that inhibitory recruitment, we hypothesized that overexpressing neuronal pentraxin 2 (NPTX2 or Narp) in the LEC of cognitively impaired aged rats would restore excitatory/inhibitory (E/I) homeostasis in the hippocampus, leading crucially to better memory function in those rats. NPTX2 is a synaptic protein that is secreted presynaptically in an activity-dependent manner to recruit excitatory synapses on parvalbumin interneurons to increase inhibitory drive. In the present study, we tested this hypothesis using aged Long-Evans rats (25-28 mo old, n = 12) that were screened in a standardized assessment of spatial cognition before initiation of experimental treatments. Rats that showed cognitive impairment were selected for viral vector transduction in the LEC with

AAV-CaMKII-NPTX2-HA-V5 or AAV-CaMKII-GFP control. A month after surgery, the rats were trained over three days in a hippocampal-dependent water maze task to locate a hidden escape platform. The rats were tested 24 hr after the end of training for their long-term memory. Unlike those in the GFP control group, the aged rats treated with NPTX2 showed memory for the location of the escape platform as measured by a greater time spent and a higher number of crossings in the target annulus compared to the control annulus. The rats in the NPTX2 group also had shorter swim latencies than the control rats to find the location of the escape platform during the memory test. These results indicated that the upregulation of NPTX2 in the LEC to engage a greater inhibitory function in the hippocampus improved age-associated memory performance in a hippocampal-dependent task, consistent with the recent findings at the *in vitro* level that the overexpression of NPTX2 in the LEC remediates hippocampal E/I imbalance due to aging (Moreno et al., 2023, SfN poster).

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Poster

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Program #/Poster #: PSTR371.15/X12

Topic: H.12. Aging and Development

Support: Intramural Research Program of the NIH, National Institute on Aging

Title: Assessment of Fisher 344 rats as a model to examine the role of sleep in age-related cognitive outcome

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Abstract: Accumulating evidence indicates that age-related changes in sleep quality and quantity contribute to increased risk of Alzheimer's disease and cognitive impairment later in life. At present, however, our ability to identify the cellular and molecular mechanisms that link sleep and age-related cognitive decline are limited in large part by the lack of animal models that reliably recapitulate relationships observed in humans. Given the long lifespan in humans, a valid preclinical model would also facilitate longitudinal study designs that examine whether sleep earlier in life affects cognitive outcome later in life, and moreover, would offer a means to identify interventions aimed at slowing, stopping, or even preventing age-related cognitive decline. To that end, we focused on Fisher 344 rats, which are the most widely used rat strain in aging research, are provided by the National Institute on Aging (NIA) as a resource to facilitate aging research. Here we tested young (~6 months; N = 8 males, 10 females) and aged (~23 months; N = 11 males, 10 females) rats in a hippocampus-dependent version of the Morris water maze. Spatial memory capacity was assessed by means of a learning index (LI) score, which was

calculated as the weighted average proximity to the hidden escape location across probe trials. We observed that, on average, young rats performed significantly better than aged rats ($p<0.0001$), where only two aged rats performed within the range of young. These data suggest that F344 rats may be particularly well-suited to assess cognitive impairment. Young male and female rat LI scores did not significantly differ ($p=0.86$), nor did LI scores between aged male and female rats ($p=0.23$). Next, we recorded EEGs and EMGs from these rats to assess sleep quantity (both REM and NREM) and quality. These analyses are ongoing. Together these data will allow us to determine whether Fisher 344 rats may be a useful model to examine the neurobiological basis connecting sleep and cognitive outcome later in life.

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Poster

PSTR371: Learning and Memory in Aging

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Topic: H.12. Aging and Development

Support: RO1AG037868
P30CA177558

Title: Ex vivo hippocampal transcriptome response to corticosterone in young and aged female F344 rats

Authors: *D. R. CRAIG, E. M. BLALOCK;
Pharmacol. & Nutritional Sci., Univ. of Kentucky, Lexington, KY

Abstract: Title: Ex vivo hippocampal transcriptome response to corticosterone in young and aged female F344 ratsAuthors: D. R. Craig, E. M. BlalockRationale & ObjectiveGlucocorticoid (GC) signaling is thought to play a key role in stress' negative impact on brain aging (BA). Several lines of evidence indicate that psychosocial stress and stress hormone exposure accelerates BA. In prior work, using *ex vivo* slice preparations of dorsal (DHIP) and ventral hippocampus (VHIP), we examined transcriptional signaling properties of the GC-driven, downstream effector molecule, Sgk1, which was increased by both stress and aging. DHIP is thought to play a more prominent role in spatial navigation and short-term memory, while VHIP provides feedback inhibition of the stress response. Here, an *ex vivo* HIP slice preparation was used to examine the differential GC-driven transcriptome in DHIP and VHIP from young and aged (n = 3/age) female Fisher 344 rats to test the hypotheses that: *Ex vivo* GC exposure changes mRNA levels in expected directions (e.g., elevated Sgk1, suppressed Tnf), this effect differs between DHIP and VHIP, and young tissue will show a greater response than aged. Analysis of an additional experiment (n = 5/age) with comparable experimental dynamics is in preparation.MethodsHIP slices were mapped according to their longitudinal position (D or V) and maintained in oxygenated artificial cerebrospinal fluid at 32 ± 1°C in four-well interface

chambers, and incubated in either 0.1% DMSO (vehicle control) or 3.5 µM corticosterone for 2-hrs. Slices were then removed and RNA was purified. After quality control, whole transcriptome RNA sequencing was performed (Illumina HiSeq) using a dual indexed, paired end, strand-specific read-strategy with ~25 million reads/sample. Resulting count data were analyzed for Dorsal vs Ventral, Young vs Aged, and Control vs Cort effects using DeSeq2. Results & ConclusionsIn this preparation, the well-established aging transcriptional signature was highly similar in DHIP and VHIP. DHIP transcriptional profiles were relatively unaffected by GC exposure regardless of animal age. In VHIP, there were significantly more genes than expected by chance that were both regulated by GCs in young subjects, as well as changed with age in control subjects. Genes commonly regulated by both aging and GC exposure in VHIP, showed a highly similar direction and magnitude of change; suggesting that aging may upregulate the expression of GC-driven mRNAs, producing a ceiling-effect above which GCs cannot further drive expression. Finally, as expected, in both DHIP and VHIP, well-defined GC-driven mRNAs were increased, while GC-suppressed mRNAs were decreased.

Disclosures: D.R. Craig: None. **E.M. Blalock:** None.

Poster

PSTR371: Learning and Memory in Aging

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.17/X14

Topic: H.12. Aging and Development

Title: Investigation and regional mapping of the molecular signatures underlying memory formation and age-related memory loss

Authors: *A. KOKKOSIS[1], Y. BAI[2], D. VERGATA[3], B. ZAMBROWICZ[1], E. PAVLOPOULOS[1];
[1]Velocigene, [2]Mol. Profiling and Data Sci., [3]Therapeut. Proteins, Regeneron Pharmaceuticals, TARRYTOWN, NY

Abstract: Long-term memory (LTM) is a learning-dependent process which occurs in the hippocampus and requires the activation of gene expression and *de novo* synthesis of synaptic components critical for synapse strengthening and new synapse formation. Although a sound foundation is in place, we are still at the initial stages of understanding the regulatory mechanisms underlying LTM and how they are affected by aging, and lead to cognitive decline and memory loss. Here, we used snRNA-Seq to investigate both baseline and learning-induced molecular mechanisms in the mouse hippocampus in a region-specific and cell-type specific manner, in combination with examination of different degrees of memory decline. To test hippocampal-dependent memory, we used the novel object recognition task (NOR). To examine aged mice that exhibit memory impairment and also associate molecular changes with the severity of memory loss, we developed a behavioral paradigm consisting of two sequential NOR tasks, one week apart from each other. We demonstrated highly significant correlation of animal

performance between the two tasks and consistently found all aged mice (22 months) to exhibit significantly lower memory compared to young animals (5 months). Notably, the aged mice were distinguished into two groups: those with severe memory loss (~80% of animals), and those with moderate memory deficits (~20%), consistent with the differential memory decline observed in humans. For our snRNA-Seq study, a new cohort of naïve mice was subjected to the first NOR for LTM assessment and stratification of the aged animals into the two groups. One week later, the majority of the mice underwent the training (learning) phase of the second NOR task and their hippocampi were isolated one and five hours post-training, the time window during which learning-mediated transcriptomic changes underlying LTM are thought to occur. The rest of the animals did not undergo the training phase and were used as baseline controls. We performed snRNA-Seq on three FACS-enriched populations: activated neurons (cFOS and/or ARC positive), non-activated neurons, and non-neuronal (NeuN negative) populations. Both age-groups displayed a significant increase of activated hippocampal neurons after learning. We identified >50 distinct neuronal and non-neuronal supertype clusters, confirmed a significant cell-type specific upregulation of activity-dependent genes in learning-activated neurons, established a transcriptional map of learning-mediated differentially expressed genes in young and aged mice, and investigated the effects of aging on these molecular signatures.

Disclosures: A. Kokkosis: A. Employment/Salary (full or part-time):; Regeneron Pharmaceuticals Inc. **Y. Bai:** A. Employment/Salary (full or part-time):; Regeneron Pharmaceuticals Inc. **D. Vergata:** A. Employment/Salary (full or part-time):; Regeneron Pharmaceuticals Inc. **B. Zambrowicz:** A. Employment/Salary (full or part-time):; Regeneron Pharmaceuticals Inc. **E. Pavlopoulos:** A. Employment/Salary (full or part-time):; Regeneron Pharmaceuticals Inc..

Poster

PSTR371: Learning and Memory in Aging

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.18/X15

Topic: H.12. Aging and Development

Support: This research was supported entirely by the Intramural Research Program of the National Institutes of Health, National Institute on Aging.

Title: Regional Brain Volumes Associated with Memory in Aging Rats: A Voxel-Based Morphometry Study

Authors: *S. ESSIG[1], C. COOPER[1], L. CHENG[1], K. FALCON[1], E. RADAKOVIC[1], H. LU[2], K. FISHBEIN[1], A. SHAFER[1], E. PEREZ[1], J. M. LONG[1], P. R. RAPP[1];
[1]Natl. Inst. on Aging, Baltimore, MD; [2]Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Cognitive aging is generally accompanied by reductions in regionally specific grey matter volumes (GM). Our lab previously demonstrated in humans and rhesus monkeys that

decreases in medial temporal lobe, prefrontal cortex, and cerebellum volumes correlated with memory. Yet, it is unknown whether these brain-behavior relationships translate to preclinical rodent models of neurocognitive aging, which are a valuable resource for investigating regional cellular and morphological changes in relation to memory. To bridge this translational gap, we sought to answer the following questions: (1) do regional brain volumes in rodents change with age and in relation to cognitive status, and (2) do the regional volumes that correlate with memory change with age? We used the Morris water maze (MWM) to characterize spatial memory in young (6 months, n=11) and aged (24 months, n=22) male Long-Evans rats. T2-weighted structural MRI scans were acquired on a Burker 9.4T scanner, skull-stripped, aligned, and segmented GM was normalized to a common space for voxel-based morphometry (VBM) analysis. In contrast to a long history of neuroanatomical research in human aging but consistent with the limited number of longitudinal neuroimaging data in rodents, aged rat brains were significantly larger than young adults with marked expansion of the cortical mantel. Nonetheless, among the aged animals alone, the volumes of multiple regions implicated in spatial memory, including the hippocampus and frontal cortex, were positively correlated with water maze performance. Regional volume associations with memory also extended to the cerebellum, reminiscent of recent observations in monkeys and humans. Analyzing interaction effects confirmed that the associations between spatial memory and volumes in the hippocampus and cerebellum subregions are age-dependent. These results address a translational gap by extending the regional distribution of GM volumes coupled with memory to a rodent model of neurocognitive aging, including regions less noted for memory, like the cerebellum. Future studies will investigate regional micro-scale, cytoarchitectural changes in the cerebellum that may undergird its association with cognitive aging.

Disclosures: S. Essig: None. **C. Cooper:** None. **L. Cheng:** None. **K. Falcon:** None. **E. Radakovic:** None. **H. Lu:** None. **K. Fishbein:** None. **A. Shafer:** None. **E. Perez:** None. **J.M. Long:** None. **P.R. Rapp:** None.

Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.19/X16

Topic: H.12. Aging and Development

Support: Neuroscience Program, the Office of Research and Graduate Studies, the College of Medicine, the John G. Kulhavi Professorship in Neuroscience, and the E. Malcolm Field and Gary Leo Dunbar Chair in Neuroscience at Central Michigan University

Title: Gender Differences in Cognitive Performance in Progesterone-Treated Young and Aged C57 Mice

Authors: *O. SMITH[1], D. DOYLE[2], J. ROSSIGNOL[3], K. A. JENROW[4], G. L. DUNBAR[5], L. GARMO[6,1], K. REED[7];

[1]Neurosci., [3]Col. of Med., [4]Psychology, [5]Psychology/Program in Neurosci., [2]Central Michigan Univ., Mount Pleasant, MI; [6]; [7]Auburn, MI.

Abstract: Progesterone is a neurosteroid and sex hormone, which has been shown to provide neuroprotective effects in brain-damaged mice. Less is known about its effects in healthy mice, especially concerning potential gender differences. The objective of this study was to assess how progesterone affects cognitive function in both young and aged male and female C57 mice. Male and female mice, ranging from 4 to 9 months old for the young group and 20 to 25 months old for the old group, received daily subcutaneous injections of either progesterone (5 mg/kg) or a vehicle solution (30% 2-hydroxy beta-cyclodextrin) for 56 days. Cognitive evaluations were performed utilizing the water-T-maze and passive avoidance behavioral tasks. Our results indicate that progesterone-treated young males were able to complete the water T-maze task more efficiently than young progesterone-treated females. Effects of progesterone treatments on aged males or females revealed no significant differences in either of the cognitive tasks. Surprisingly, progesterone-treated young female mice had fewer successful completions on the water-T-maze task relative to vehicle-treated young females. These finding suggest that progesterone my confer some cognitive enhancements in young male mice, but may be detrimental for learning in young female mice. It is hypothesized that the addition of exogenous progesterone may have interfered with endogenous levels of progesterone in the young females, decreasing their ability to solve the cognitive task. Further research looking at progesterone receptors and inflammatory markers in both young and aged female and male C57 mice should help explain these findings.

Disclosures: O. Smith: None. **D. Doyle:** None. **J. Rossignol:** None. **K.A. Jenrow:** None. **G.L. Dunbar:** None.

Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.20/X17

Topic: H.12. Aging and Development

Support: NIH R01 AG037868

Title: New Onset Chronic Psychosocial Stress at Different Ages in Female F344 Rats

Authors: *K. BRETLAND, I. DJURICIC, D. R. CRAIG, E. M. BLALOCK;
Pharmacol. and Nutritional Sci., Univ. of Kentucky, Lexington, KY

Abstract: A recent report by The American Psychological Association indicates that the social isolation and restriction of movement associated with the COVID-19 pandemic acted as a chronic psychosocial stressor (CPS). CPS has been shown to exacerbate, and possibly accelerate, age-related pathologies (e.g., immune, cardiovascular, and neurodegenerative). The prevalence of these conditions is projected to increase as the U.S. population ages: the 2020 U.S Census

reports 17% of U.S. population are above age 65, with an expected increase to 25% by 2060. However, despite years of research clearly showing that aspects of aging are accelerated by psychosocial stress, little work has investigated the age-course of the stress response or the consequences of new onset CPS at different ages in female animal models of aging. Previous animal work (including hippocampal transcriptional profiling, blood corticosterone measures, and Morris water maze testing) show that psychosocial stress accelerates brain aging in young, but not aged, animals. To address this knowledge gap, in the present study, female Fischer 344 rats of four different ages (3M, 6M, 12M, and 18M) were restrained for 3 months (4d/wk, 3hr/day). During the first, middle, and last week of stress, novel object recognition, blood corticosterone levels, and the estrous cycle were tracked, while body weight was measured weekly. Two-weeks after the chronic restraint paradigm was completed, open field and Morris water maze were performed. Animals were cardiac perfused with 4% PFA and brains were collected for future immunohistochemistry and transcriptional profiling, while cardiac blood was collected (prior to PFA) to measure hormones levels via mass spectrometry. As expected, body weight increased, maze performance declined, and there was a marked shift in the estrous cycle with age. Further, the behavioral response to CPS changes with age, showing a greater negative effect in young adult animals.

Disclosures: K. Bretland: None. **I. Djuricic:** None. **D.R. Craig:** None. **E.M. Blalock:** None.

Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.21/X18

Topic: H.12. Aging and Development

Support: NIH Grant 1R01NS121220

Title: Elderly Aplysia's rhythmic escape behavior develops behavioral and cognitive deficits that can be partially restored using repeated stimulation or pharmacological intervention

Authors: *V. K. MISTRY[1], D. MARTINEZ[2], W. N. FROST[3];
[1]Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL; [2]Colgate Univ., Hamilton, NY; [3]Stanson-Toshok Ctr. for Brain Function and Repair, Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: Aplysia californica is a sea slug that has provided major advances in our understanding of the cellular basis of behavior and learning. While studies by others have explored the cellular and molecular basis of age-related decline in several Aplysia behaviors, here we examined the impact of aging on the animal's escape locomotor behavior, which, due to its rhythmic nature, is highly amenable to network-level analyses via large-scale neural activity imaging. We tested young (5-7mo) and elderly adults (12-13mo) under both naive conditions and after a 5-trial non-associative learning protocol. Elderly Aplysia were found to perform fewer,

less vigorous locomotion cycles than young adults, and typically had lost their ability to quicken locomotion initiation across repeated stimulation trials. In preliminary experiments, elderly animals from the same egg cohort were also separable into two groups: “resilient agers”, who demonstrated degraded but intact locomotion response to an initial stimulus, and “poor agers”, who were completely unresponsive to an initial stimulus. Remarkably, stimulus repetition in “poor agers” resulted in behavioral and cognitive improvement, restoring the ability to locomote and to quicken locomotion onset across trials. Since serotonin has been shown to play an important role in Aplysia’s escape locomotion behavior, and its levels decline in the brain as animals age, we explored the effects of a single injection of the serotonin precursor 5-HTP into the body of non-responsive elderly Aplysia. Preliminary experiments found that such injections of serotonin precursor were sufficient to restore “poor ager” escape locomotion behavior to “resilient ager” naive levels within several hours. These findings represent the first characterization of age-related decline in Aplysia’s escape locomotion behavior and its modification by non-associative learning, and open up opportunities for exploring the network basis of this decline, as well as therapeutic options for restoring function. They also lay the groundwork for explorations of network-level differences that might explain why some animals age better than others with regard to motor and cognitive function.

Disclosures: V.K. Mistry: None. **D. Martinez:** None. **W.N. Frost:** None.

Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.22/X20

Topic: H.12. Aging and Development

Support: MSCA Grant "SmartAge" 859890

Title: Comparing physical activity regimens: impact on cognitive decline in aging mice

Authors: *R. PETIT[1], F. HAAS[1], M.-L. EDERER[2], M. HAASE[1], J. LINDNER[1], R. SIMON[1], C. FRAHM[1];
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Abstract: The global shift towards an aging population emphasizes the urgency of addressing cognitive impairments in older adults. This study investigates the impact of different physical activity paradigms on cognitive functions in aged male C57BL/6J/Ukj mice. Specifically, we compare the effects of 24/7 voluntary wheel running with a regimen of thrice-weekly training, initiated at 18 months and tested at 20 months—a critical period when cognitive decline in mice becomes apparent. Due to the need to isolate mice for individual running performance assessment, control groups were also isolated.Results reveal that 24/7 running leads to spatial learning improvement assessed over a 6-day training period in the Barnes Maze task.

Additionally, enhancements were observed in short- and long-term memory (probe trial and retention test), as well as cognitive flexibility (reversal test). However, when mice ran only three nights per week, no cognitive improvement was observed in any test, despite achieving good running performance. Additionally, we examined whether alternating isolation in the control group could lead to stress associated with a decline in cognitive function. To this end, we compared our isolated control group with those from mice housed in groups. No such stress effects were observed, confirming the validity of our control group. These results suggest that daily, rather than 3 times a week, alternating activity may be required to improve cognitive abilities in aging mice.

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Poster

PSTR371: Learning and Memory in Aging

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.23/X21

Topic: H.09. Spatial Navigation

Title: Impact of Social Isolation on Cognitive and Motor Functions in Aging Male Mice

Authors: R. SIMON, M. HAASE, J. LINDNER, F. HAAS, ***C. FRAHM**;
Jena Univ. Hosp., Jena, Germany

Abstract: The global demographic shift toward an aging population raises concerns about the increasing prevalence of social isolation (SI) among older adults, a concern further highlighted by the recent COVID-19 pandemic. SI is associated with increased risk of depression, anxiety, and cognitive impairment, exacerbating the global health issue of age-related cognitive decline. Studies on the effects of social isolation in older animals are scarce, but in humans, the detrimental effects become more pronounced with age, with a particularly strong effect on males. In our study, male C57BL/6J/Ukj mice were isolated at 20 months of age for either 4 or 8 weeks. During the last 2 weeks of isolation, cognitive and motor function analyses were performed using the Barnes Maze and RotaRod tests, respectively. Post-isolation evaluations showed no significant differences in motor function based on social isolation, regardless of its duration, whether short or long. All cognitive parameters tested (learning, short and long-term memory, cognitive flexibility) were impaired after 8 weeks of isolation, while a 4-week period showed no discernible effects, in each case compared to group-housed controls. Our research indicates that cognitive impairment onset is dependent on the duration of isolation, with noticeable effects after 8 weeks. These results highlight the critical time-dependent nature of social isolation's impact on cognitive health. Further investigation is essential to develop effective interventions that can mitigate the risks associated with prolonged social isolation.

Disclosures: R. Simon: None. **M. Haase:** None. **J. Lindner:** None. **F. Haas:** None. **C. Frahm:** None.

Poster

PSTR371: Learning and Memory in Aging

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.24/X22

Topic: H.12. Aging and Development

Support: NS113804
GM121231

Title: Aging impairs acquisition of paired associate learning in Long Evans rats

Authors: *C. WEISS[1], T. G. LAUGHLIN[2], Z. SONG[3], A. GALVEZ[1], M. PACHICANO[1], A. S. WIDGE[4], J. L. VOSS[5], J. F. DISTERHOFT[2];
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Abstract: Multiple sessions of non-invasive transcranial magnetic stimulation administered to the human hippocampal network has been shown to facilitate memory formation and functional connectivity in a paired associate memory task (Wang et al., 2014; Hermiller et al., 2019). To understand neural mechanisms that mediate the stimulation-induced effects in human subjects, we trained rats in an object-location paired associate learning (PAL) task (Bussey et al., 2008), a form of PAL that is used in human studies. Rats were first trained to eat from the pellet trough, then rewarded for nose-poking anywhere on the screen, then gradually shaped to nose-poke one of three segments along the top of the screen using an automated touchscreen system and schedules described by Smith et al. (2022). The PAL schedule was then initiated. We used the version of the paradigm where two of three different visual cues are presented in two of three possible screen positions (left, center, right). Only one of the 6 possible combinations of the 3 cues and 3 screen positions was rewarded during training. The present study sought to examine the effect of aging on acquisition of PAL to a criterion of 80% correct for two consecutive sessions. We used the image set “flower, spider, plane” of many dPAL studies with rodents (Horner et al., 2013). We used male and female Long Evans rats from 3-18 months of age at the start of training. Rats were assigned to 3-5m (N=15), 7-9m (N=19), or 15-18m (N=6) for analysis (1 young rat was a statistical outlier and excluded). A Kruskal-Wallis test revealed a significant effect of age (p=0.01) for the number of sessions to criterion with mean ranks of 6.6, 16.4, and 19.5 for the 3 age groups respectively. The mean number of sessions to criterion for the 3 age groups was 7.3, 20.1, and 18.0, (note that most rats in the 15-18m group were stopped at 20 sessions, a criterion we came to adopt; although 1 rat required only 9 sessions). The long-term goal of this study is to characterize and understand neural mechanisms within the cortico-hippocampal network that mediate this associative learning task, and to optimize the timing and

pattern of cortical afferent stimulation to facilitate learning and memory. After these baseline data are collected, the efficacy of different stimulation protocols can be determined by recording and tracking neuronal activity within the network, and by tracking behavioral performance across training sessions for rats of different ages.

Disclosures: C. Weiss: None. **T.G. Laughlin:** None. **Z. Song:** None. **A. Galvez:** None. **M. Pachicano:** None. **A.S. Widge:** None. **J.L. Voss:** None. **J.F. Disterhoft:** None.

Poster

PSTR371: Learning and Memory in Aging

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Topic: H.12. Aging and Development

Support: NIH Grant R01-AG028271

Title: Post-operative Cognitive Dysfunction is Exacerbated in a Model of Alzheimer's Disease

Authors: *J. BLACKWELL[1], S. MACKEY-ALFONSO[1], M. BUTLER[2], R. M. BARRIENTOS[1];
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Abstract: Post-operative cognitive dysfunction (POCD) is the persistent form of post-operative delirium, a noticeable deterioration in cognitive abilities that occurs abruptly following surgery. Persistent POCD has been largely associated with older individuals, posing an increased risk for the development of Alzheimer's disease (AD). It is known that laparotomy (exploratory abdominal surgery) combined with opioid treatment in aged rats produces memory impairments lasting at least 8 weeks, however the mechanisms underlying the development of dementia are unknown. Thus, the purpose of this study was to characterize POCD in a mouse model of AD and identify a possible mechanism. Using the same laparotomy procedure and morphine dose (2mg/kg, i.p) from our previous work in rats, surgeries were performed on 3xTg-AD mice at 3 months old with a battery of cognitive behavioral tests 2 weeks post-surgery. Preliminary findings suggest an exaggeration of POCD in 3xTg-AD compared to non-Tg mice *via* an impairment in hippocampal-dependent memory assessed by the novel location recognition test. These findings provide a possible avenue of future exploration to identify the mechanism contributing to POCD in a model of AD.

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Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.26/X24

Topic: H.12. Aging and Development

Support: R01 AG072714
5T32AG061892-04

Title: Differential effects of chronic oral THC consumption in young and aged rats

Authors: *S. ZEQUEIRA[1], E. GAZAROV[1], A. SENETRA[1], A. SHARMA[4], R. SUN[2], C. R. MCCURDY[1], B. SETLOW[3], J. L. BIZON[5];
[2]Biochem. and Mol. Biol., [3]Dept. of Psychiatry, [1]Univ. of Florida, Gainesville, FL; [4]Pharmaceutics, Dept. of Pharmaceutics, Col. of Pharmacy. Univ. of Florida, Gainesville, FL 32610, Gainesville, FL; [5]Neurosci., Univ. of Florida Dept. of Neurosci., Gainesville, FL

Abstract: With the increased legalization of recreational and medicinal cannabis, use is growing rapidly amongst older adults. As the number of older adults in the US is expected to reach 90 million by 2050, it is imperative to better understand the cognitive impacts of cannabis use in this population. We evaluated the effects of chronic oral administration of delta-9-tetrahydrocannabinol (THC; the primary psychoactive component of cannabis) on a delayed response task that assessed PFC-dependent working memory and on the Morris water maze task that assessed hippocampal-dependent spatial memory in young adult (5 months) and aged (23 months) Fischer 344 x Brown Norway F1 hybrid rats of both sexes. Rats were initially trained on the delayed response task until reaching stable performance prior to drug administration. As expected, aged rats were impaired relative to young adults, particularly at longer delays. Rats of both ages then consumed either plain gelatin or gelatin containing 1 mg/kg THC daily in their home cage. Working memory performance was assessed after three weeks of daily consumption. There were no effects of THC on working memory in young adults; however, aged rats consuming THC performed reliably better than aged rats consuming control gelatin. Rats were then trained on the water maze while continuing to consume gelatin following daily training; however, THC did not enhance spatial learning in either age group. These findings suggest that THC does not impair and can provide benefit to cognition in older subjects. While data showing pro-cognitive effects of THC in older subjects are of particular interest, the neural mechanisms underlying such effects are poorly understood. Changes in glucose utilization and metabolism within the CNS are well documented with age and are linked with cognitive decline as well as neurodegenerative conditions such as Alzheimer's disease. To better understand the relationship between brain metabolism and cannabis use, a second experiment testing the effects of chronic oral THC consumption on brain metabolism in aging was done using Matrix-assisted laser desorption/ionization mass spectrometry (MALDI Imaging). For this study, young and aged rats consumed control or THC gelatin for three weeks, after which they were euthanized for brain tissue collection and processing. Initial results indicate that chronic oral THC causes brain region-specific alterations in levels of a range of small molecules, notably among those associated with monoamine metabolism in prefrontal cortex.

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Poster

PSTR371: Learning and Memory in Aging

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Program #/Poster #: PSTR371.27/Web Only

Topic: H.12. Aging and Development

Support: No 028-COVID-19/2022-OAJ-UAC, resolution: N° 015-CU-2022-UAC, Universidad Andina del Cusco.

Title: Reversal of cognitive aging: contribution of LTCC blockade

Authors: P. ORURO, ***E. ORURO**;
Inst. Cientifico, Univ. Andina del Cusco, Cusco, Peru

Abstract: Background: A variety of mechanisms of brain aging havebeen described from the intrinsic excitability of neurons, considering themodification of afterhyperpolarization as a potential restorative agent incognitive aging. Activation of calcium-dependent potassium channels correlateswith afterhyperpolarization (AHP) linked to the firing frequency of a pyramidalneuron of the hippocampal CA1 region, vulnerable to the aging process .Increased intracellular calcium is a key factor in a wide variety of neurologicaldeterioration processes, particularly in cognitive aging . At the behaviorallevel, it has been demonstrated that the blockade of L-type voltage-dependentcalcium channels (B-LTCC) is able to restore the spatial discrimination indexof aged rats to the level of adult rats, observing a dual effect of B-LTCC inthe hippocampus under an inflection age that determines the rectification ofits possible facilitation or depression of learning . However, the interactionof neurons with B-LTCC-conditioned restoration of their intrinsic properties atthe neuronal network level is unknown. In the present work, we explore whetherthere is a difference in activity dynamics between the aged CA1 neuronalnetwork with neuronal electrophysiological modifications attributed to B-LTCCand the adult CA1 neuronal network. **Methods:** Using electrophysiologicalparameters of adult and aged neurons of the hippocampal CA1 region implementedin an Integration and Firing model, with a modified Jensen-Idiart-Lismanplasticity model, in a Watts and Strogatz network, we compared learning in anadult, an aged control and an LTCC-blocked (B-LTCC) neural network, configuring280 neurons for each group. **Results:** Comparing number of spikes beforeand after training, a difference is observed for the adult ($p<0.0001$ $t=265.6$), aged ($p<0.0001$ $t=19.70$) and aged with B-LTCC ($p<0.0001$ $t=17.12$)groups. There is a significant difference in the number of spikes following thetraining protocol between the logs of 10 simulations of an adult and an agednetwork ($p<0.0001$ $t=317$) with a mean difference of -231412 ± 728.2).Likewise, a significant difference is evident for the adult vs aged networkwith nimodipine (<0.0001 t=306.0). **Conclusions:** Our simulationssupport the established behavioral change in aging, however we suggest thatB-LTCC-induced AHP modification is not a sufficient factor to reverse cognitiveaging in a hippocampal network. More studies are needed to test major changesin AHP that contribute to significant values in learning modification.

Disclosures: P. Oruro: None. **E. Oruro:** None.

Poster

PSTR371: Learning and Memory in Aging

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR371.28/X25

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

Title: Assessment of memory with a continuous recognition task (MemTrax) and subjective function

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Abstract: Alzheimer’s disease is highly related to memory dysfunction. Alzheimer pathology initially affects long cortically-projecting brainstem neurons, which manage the brain’s neuroplasticity, including synaptogenesis and removal of synapses made obsolete by new information being encoded. The loss of brainstem input to the cortex impairs synapse management and the integrity of critical neurons, adversely affecting episodic memory. The presence and extent of pathological changes can be estimated by assessing an individual’s capacity to process and encode complex information. While numerous approaches to cognitive assessment provide approximate measures of Alzheimer impairment, a precise approach to determining Alzheimer-type memory dysfunction is the continuous recognition task (CRT). MemTrax is an engaging 2-minute online CRT in which instructed participants attend to 50 complex visual images and detect 25 repetitions. MemTrax strongly and efficiently assesses a participant’s ability to attend to a stimulus, learn its complex information, and recognize the image later, with additional metrics of the rate and variability of response processing. There are two types of correct responses to a stimulus: HIT (subject responds when match occurs) or correct rejection (CR, subject does not respond when there is not a match); and two types of incorrect responses: MISS (subject does not respond when a match occurs) or false alarm (FA, subject responds when no match occurs). MemTrax shows small but significant changes with age and is at least as accurate in measuring Alzheimer-related cognitive problems as the Montreal Cognitive Assessment (MoCA). MemTrax data suggest that RTs for HITs decreased on trials with more FAs, and RTs for HITs increased on trials with more MISSes for participants of all ages. When provided online, male participants and female participants perform similarly, though more female participants than male participants of all ages voluntarily and anonymously

participated. Female and male participants of all ages have similar sensitivities to their subjective experiences of their internal states related to their subjective cognitive dysfunctions (SCD). Male and female participants only expressing concerns about their memory had slower RTs for hits on trials with fewer of FA errors. While male and female participants of all ages performed more misses than false alarms, their RTs and accuracy both increased with age, suggesting that effort is expended to deploy resources that enable instruction to direct cognitive processes that compensate for age effects on the quality and distinctiveness of the responses to the information.

Disclosures: J.W. Ashford: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MemTrax, LLC. **J.O. Clifford:** None. **C.B. Ashford:** A. Employment/Salary (full or part-time):; Cognifit, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MemTrax, LLC. **N.S. D'Souza:** None. **N. Bilger:** None. **M.F. Bergeron:** None. **F. Tarpin-Bernard:** None. **P.J. Bayley:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.01/X26

Topic: H.13. Schizophrenia

Title: Carpolobia lutea ethanol extract reverses drugs-induced schizophrenia-like symptoms in mice via oxido-inflammatory and neurotransmitters' pathways

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Abstract: Background: Carpolobia lutea has previously been used ethnomedicinally to treat a variety of ailments, including neurological disorders. Meanwhile, homeostatic dysregulations of neurotransmitters, neuroinflammatory cytokines and oxidative-nitrosative biomarkers are implicated in schizophrenia (SCZ). To establish the antipsychotic-like activity of the ethanol extract of C. lutea (EECL) & the underlying mechanisms of action, we challenged mice with psychotomimetic agents such as amphetamine, apomorphine, or ketamine. Methods: In acute studies, EECL (100, 200, 400, 800 mg/kg), haloperidol (1 mg/kg), clozapine (5 mg/kg) and vehicle (10 mL/kg) were orally administered 60 min before the mice were exposed to amphetamine (5 mg/kg; i.p.), apomorphine (2 mg/kg; i.p.), or ketamine (10, 30, 100 mg/kg i.p.) models of SCZ. Furthermore, in a 14-day chronic study, mice were given either vehicle (10 mL/kg; p.o.) or ketamine (20 mg/kg; i.p.), with reversal treatments with EECL, haloperidol, and clozapine beginning on day 8. Behavioural characterizations that serve as predictors of SCZ-like symptoms were extracted during the experiments in both acute and chronic studies. Afterwards,

neurochemical & histopathological determinations were processed in the brain tissues of mice that participated in a chronic study. Catalepsy testing and high-performance liquid chromatography (HPLC) analyses of EECL were all done separately. Results: The results revealed that treatment with EECL (200, 400, and 800 mg/kg; p.o.) markedly reduced the following: amphetamine- & ketamine-induced hyperlocomotion, amphetamine- and apomorphine-induced stereotypy, ketamine-induced behavioural despairs and cognitive impairment. The 7-day reversal treatment with EECL also significantly reversed ketamine-induced neurochemical changes in DA, Glu, NE, 5-HT, AChE, MDA, CAT, SOD, GSH, nitrite, IL-6, and TNF levels/activities. Furthermore, EECL prevented ketamine-induced neuronal alterations in the prefrontal cortex, hippocampal proper & cerebellum sections of the brain. EECL had a lower proclivity to induce catalepsy or extrapyramidal symptoms. Based on the HPLC analysis, EECL contained rutin, gallic acid & p-coumaric acid. Conclusions: The endpoint of these findings suggest that EECL reduces the cardinal symptoms of SCZ by modulating the oxido-inflammatory and neurotransmitter-related pathways, and the presence of various bioactive compounds may be responsible for its antipsychotic-like activity against SCZ-like symptoms. Therefore, more investigation into the specific bioactive constituents of the extract that has an antipsychotic-like effect is required.

Disclosures: N.A. Omeiza: None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.02/X27

Topic: H.13. Schizophrenia

Title: Suvn-l3307032, a Positive Allosteric Modulator (PAM) at Muscarinic M4 Receptor for the Treatment of Psychotic Symptoms.

Authors: *R. ABRAHAM, V. GOURA, R. KALLEPALLI, P. JAYARAJAN, A. SHAIKH, K. BOJJA, R. BADANGE, K. BITRA, N. GUDURU, A. DAS, A. SREE, H. BOBBILI, S. PETLU, R. SUBRAMANIAN, R. SHYAM, Y. YASHASWI, R. NIROGI;
Suven Life Sci., Ltd., Hyderabad, India

Abstract: The muscarinic 4 acetylcholine receptor (M4) has been implicated in neurological disorders such as schizophrenia and cognition. Currently, the allosteric site rather than the orthosteric site is being targeted in drug discovery to avoid the cholinergic side effects. SUVN-L3307032 is a new chemical entity that has an affinity for the allosteric site of M4 receptors. The effects of SUVN-L3307032 on the allosteric site of the M4 receptor were evaluated using a cell-based reporter gene assay. The pharmacokinetic properties of SUVN-L3307032 were evaluated in both rats and dogs. Receptor occupancy studies were done using Wistar rats at doses of 3, 10, 30, and 60 mg/kg, p.o. Dopamine turnover assay was performed in male Wistar rats at doses of 10 and 30 mg/kg, i.p. The efficacy of SUVN- L3307032 to reverse amphetamine-induced

hyperlocomotion was investigated in an open-field study using male Wistar rats. SUVN-L3307032 was administered orally in the open field studies and amphetamine was administered subcutaneously (n=8 per group). To assess the effect of SUVN-L3307032 on motor function, SUVN-L3307032 was assessed separately in rotarod and catalepsy studies. SUVN-L3307032 was further assessed for safety in preliminary toxicity studies that were conducted in rats and dogs. SUVN-L3307032 was found to be a positive allosteric modulator of muscarinic M4 (M4PAM) receptor when assessed for its activity towards muscarinic receptor subtypes. SUVN-L3307032 showed oral bioavailability in rats and dogs. It was found to have brain penetration with an adequate free fraction in rat brain. SUVN-L3307032 showed dose-dependent receptor occupancy at tested doses of 3, 10, 30, and 60 mg/kg. At the tested doses, SUVN-L3307032 demonstrated an increase in dopamine turnover modulation in the cortex and striatum. In the open field studies, SUVN-L3307032 attenuated amphetamine induced hyperlocomotion. The observation from the amphetamine induced hyperlocomotion assay correlated with the occupancy at the allosteric site of muscarinic M4 receptors. The administration of SUVN-L3307032 did not exhibit catalepsy-like behavior. Likewise, administration of SUVN-L3307032 had no significant effect on the latency to fall in the rotarod test. Preliminary toxicity studies did not show any concerns for development. Hence, SUVN-L3307032 is currently being progressed for further development.

Disclosures: R. Abraham: A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **V. Goura:** 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. Jayarajan:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **A. Shaikh:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **K. Bojja:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **R. Badange:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **K. Bitra:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **N. Guduru:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **A. Das:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **A. Sree:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **H. Bobbili:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **S. Petlu:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **R. Subramanian:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **R. Shyam:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **Y. Yashaswi:** 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

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.03/X28

Topic: H.13. Schizophrenia

Support: r01mh134466
r01mh120118

Title: Restoring Cognitive Function in mouse models of Schizophrenia: Targeting inhibitory signaling in the Prefrontal Cortex

Authors: *N. BAJWA[1], A. MUKHERJEE[2], J. SCOTT[3], T. NISHI[6], S. J. MOSS[4], M. HALASSA[5];
[1]Univ. of Helsinki, Helsinki, Finland; [2]Neurosci., Tufts Univ., Boston, MA; [3]Tufts Univ., Cambridge, MA; [4]Tufts Univ., Boston, MA, ; [5]Tufts Univ., Boston, MA; [6]Ovid Therapeut., Fort Lee, NJ

Abstract: Cognitive impairments in psychiatric disorders such as Schizophrenia are causally linked to atypical prefrontal cortex (PFC) function. Emerging evidence from clinical observations and animal models indicates that disruptions in the excitatory/inhibitory (E/I) balance within the PFC contribute to deficits in various cognitive domains, including working memory and cognitive flexibility. While several hypotheses have been proposed to explain the E/I imbalance in schizophrenia, dysfunctional GABAergic inhibition has emerged as a prominent candidate. However, the precise relationship between inhibitory signaling dysfunctions in the PFC and cognitive deficits is poorly understood, impeding progress in therapeutic interventions. Here we aim to bridge this gap in knowledge by unraveling the connection between GABAergic inhibition, PFC E/I balance, and cognitive dysfunction across multiple models relevant to schizophrenia.
Our findings reveal that levels of the neuronal K+/Cl- co-transporter KCC2, crucial for maintaining appropriate intracellular chloride levels for GABA-mediated hyperpolarization, are reduced in the PFC of the 22Q11 deletion syndrome (22Q11DS) mouse model of schizophrenia. Physiologically, PFC neurons in 22Q11DS mice exhibit reduced inhibition in response to both local and long-range inputs, accompanied by an increase in noisy responses to patterned stimulation. This loss of network stability in the PFC is mirrored in the impaired performance of these mice in tasks demanding working memory maintenance and cognitive flexibility. Furthermore, chronic methamphetamine (METH) administration to wildtype mice replicates the deficits observed in 22Q11DS mice, suggesting that E/I imbalance and cognitive impairments are consistent across various schizophrenia models. Establishing causality of KCC2 dysfunction, we demonstrate that selective hemizygous knockdown of the K/Cl co-transporter KCC2 in the PFC of wildtype animals reproduces the behavioral and electrophysiological deficits observed in the 22Q11DS and METH mouse models. Critical to our therapeutic objective, both the physiological and cognitive deficits observed in the 22Q11DS and METH mouse models are ameliorated by a novel selective potentiator of KCC2. These findings collectively underscore KCC2 as a promising therapeutic target for restoring cognitive function in schizophrenia across multiple models.

Disclosures: N. Bajwa: None. **A. Mukherjee:** None. **J. Scott:** None. **M. Halassa:** 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.; Ovid Therapeutics.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.04/X29

Topic: H.13. Schizophrenia

Support: Kubly Mental Health Research Center
College of Health Sciences, Marquette University
National Institute of Mental Health MH103775

Title: The KCNQ (Kv7) potassium channel regulates cognitive and negative symptoms of Schizophrenia

Authors: *L. METKO, T. MAXIM, N. ABRAHAM, C. JOHNSTON, M. GHASEMZADEH; Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: Schizophrenia (SZ) is a chronic mental disorder which affects millions of people worldwide. Changes in neural network activity may contribute to negative and cognitive symptoms of schizophrenia. Unfortunately, current FDA-approved treatments are not effective against the negative and cognitive deficits of schizophrenia. Here we have focused on the role of KCNQ (Kv7) potassium channels in regulation of negative and cognitive schizophrenia symptoms. KCNQ channels function as subthreshold potassium channels with unique properties of slow activation and non-deactivation, which render these channels particularly effective at regulating membrane potential, generation of action potentials, and neurotransmitter release. These channels regulate membrane potential and augment stimulus-evoked neurotransmitter release in the absence of changes in the basal neurotransmitter levels in the hippocampus and cortex, especially for acetylcholine. It has been suggested that these properties of the KCNQ channel may enhance signal-to-noise ratio in neural circuits and benefit cognitive processes. Our working hypothesis is that KCNQ channel blockers may be able to ameliorate the negative and cognitive symptoms of schizophrenia. This hypothesis was examined using the acute systemic phencyclidine (PCP) administration model of schizophrenia in rodents. These studies used acute phencyclidine (PCP, 1.5 mg /kg, sc) administration in adult male rats to induce negative and cognitive deficits and investigated the role of KCNQ channel in these symptoms. Systemic blockade of KCNQ channels rescued PCP-induced deficits in social interaction, novel object recognition, spontaneous delayed alternation task, and pre-pulse inhibition of startle response. Furthermore, it was demonstrated that blockade of KCNQ channels in the prefrontal cortex was effective in ameliorating the PCP-induced deficits in T-maze while blockade in nucleus accumbens was without any effect. In agreement with our hypothesis, pharmacological activation of the KCNQ channel using a channel opener (Retigabine) exacerbated the PCP mediated deficits in social interaction, spatial working memory, and prepulse inhibition of startle response. The results suggest that blockade of KCNQ potassium channels may be an effective novel strategy for ameliorating the negative and cognitive symptoms of schizophrenia. Future directions include testing this hypothesis in a sub-chronic PCP model of schizophrenia, to investigate the role of KCNQ channels in regulation of behavior in a drug-free state.

Disclosures: L. Metko: None. **T. Maxim:** None. **N. Abraham:** None. **C. Johnston:** None. **M. Ghasemzadeh:** A. Employment/Salary (full or part-time):; AviMed Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AviMed Pharmaceuticals.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.05/X30

Topic: H.13. Schizophrenia

Support: NIH Grant R01NS122840

Title: Comparison of cellular-resolution to bulk fluorescence recordings of striatal calcium activity as an imaging-based readout of clinical antipsychotic effect

Authors: *S. YUN[1], J. G. PARKER[2];
[1]Northwestern Univ., Chicago, IL; [2]Neurosci., Northwestern Univ., Chicago, IL

Abstract: *In vivo* imaging using genetically encoded sensors for calcium activity and signaling by other neurotransmitters has become a mainstay tool for many basic neuroscience research labs. In addition, our lab recently showed that in vivo imaging can inform preclinical drug development. Specifically, we used miniature microscopes to record calcium activity in striatal D1 and D2 dopamine receptor-expressing spiny projection neurons (SPNs) under normal and hyperdopaminergic conditions to mimic schizophrenia (Yun *et al*., *Nature Neuroscience* 2023). We used this approach to assay the effects of 10 different antipsychotic drugs or drug candidates. Unexpectedly, we found that the most clinically effective drugs preferentially modulate calcium activity in D1-SPNs under hyperdopaminergic conditions. Here we re-evaluated our results using a data processing pipeline to approximates a fiber photometry signal from our cellular-resolution, miniature microscope recordings. This re-evaluation is important because fiber photometry is technically simpler and less expensive than miniature microscopes, and therefore accessible to more labs. However, we know that bulk fluorescence traces of calcium activity do not reliably reflect the somatic calcium activity of individual SPNs (Legaria *et al*., Nature Neuroscience 2022). The bulk fluorescence traces we obtained by re-processing our cellular-resolution recordings of D1-SPN and D2-SPN calcium activity exhibited directional changes in response to excess dopamine that were opposite to our previous study: amphetamine treatment decreased bulk fluorescence ($\Delta F/F$) in D1-SPNs and decreased it in D2-SPNs. However, when we performed event detection on the bulk fluorescence traces and computed the rates of these bulk 'events' as a function of locomotor speed, we obtained results more consistent with our previous findings. Specifically, the rates of bulk fluorescence events were increased at higher running speeds in both SPN types, and amphetamine treatment increased the rate of events in D1-SPNs and decreased it in D2-SPNs. We also found that the effects of antipsychotic drug treatment had similar effects on the rate of these bulk fluorescence events as it did on the rates of individual

cell activity. Importantly, both analyses suggest an important role for D1-SPN modulation in clinical antipsychotic effect. Our results lay the groundwork for using simpler in vivo imaging approaches like fiber photometry to do preclinical drug screening—particularly for diseases associated with dopamine and striatal dysfunction.

Disclosures: S. Yun: A. Employment/Salary (full or part-time):; Northwestern University. **J.G. Parker:** A. Employment/Salary (full or part-time):; Northwestern University.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.06/X31

Topic: H.13. Schizophrenia

Support: This work was supported by the National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT) (No. NRF-2021R1F1A1064666)

Title: The antipsychotic drug clozapine suppresses the central insulin-induced mTOR activation through IRS1 in the mouse brain

Authors: *Y. KIM[1], S. KIM[2];
[1]Eulji Med. Center, Eulji Univ., Seoul, Korea, Republic of; [2]Dept. of Psychiatry, Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: The effects of antipsychotics on the metabolic regulatory system, such as insulin/glucose regulation, have been reported, however, their actions in the brain remain elusive. In this study, the effect of clozapine, a representative antipsychotic drug, on the central insulin-induced signaling effects were investigated. Intracerebroventricular (ICV) injection of insulin in the mouse brain reduced the peripheral blood glucose level and activated insulin receptor substrate1 (IRS1)-related signaling pathways in the prefrontal cortex (PFC) and hypothalamus (HT). Systemic administration of clozapine inhibited ICV insulin-induced hypoglycemia and brain signaling changes. Clozapine antagonized central insulin-induced changes in IRS1 phosphoryaltion; clozapine reduced tyrosine phosphorylation and increased of multiple serine residues phosphorylation of IRS1 in PFC and HT. Accompanied with IRS1 inhibition, clozapine inhibited insulin-induced activation of ERK1/2 and Akt, up-stream regulators of mTOR. As results, clozapine inhibited insulin-activated mTOR signaling evidenced by inactivation of S6 ribosomal protein and protein synthesis rate in PFC and HT. Reduced S6 phosphorylation by clozapine was evident in the neurons in the broad subregions of PFC and HT. Clozapine's inhibitory effect on insulin signaling was mediated by the activation of AMPK-Raptor signaling pathway. The findings demonstrate that clozapine inhibits insulin signaling in the brain, which could associate with the efficacy as well as metabolic adverse effects of antipsychotics.

Disclosures: Y. Kim: None. **S. Kim:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.07/X32

Topic: H.13. Schizophrenia

Support: CONAHCYT (252808) to Gonzalo Flores
ProDes (CA-120-BUAP) to Gonzalo Flores
CONAHCYT 'Estancias posdoctorales por México' (662350) to Hiram Tendilla-Beltrán

Title: Reversal of dendritic spine pathology in auditory and entorhinal cortices by atypical antipsychotics in the neonatal ventral hippocampus lesion model of schizophrenia

Authors: *H. TENDILLA-BELTRÁN[1], D. L. PEREZ OSORNIO[2], D. APAM-CASTILLEJOS[2], G. FLORES[3];
[1]Meritorious Autonomous Univ. of Puebla, Puebla, Mexico; [2]Inst. of Physiol., Meritorious Autonomous Univ. of Puebla, Puebla, Mexico; [3]Univ. Autonoma de Puebla / Inst. de Fisiologia, Puebla, Mexico

Abstract: The absence of dendritic spines in corticolimbic brain areas has long been recognized as a prominent feature of schizophrenia, supporting the hypothesis of excessive synaptic pruning within the framework of the developmental risk factor model. This notion is further substantiated by genetic studies linking alterations in synapse-related genes to the disorder. Dendritic spine pathology, characterized by decreased spine density accompanied by morphological abnormalities, stands out as a central mechanism in neurodevelopmental disorders like schizophrenia. Given that dendritic spines serve as primary sites for glutamatergic transmission, this pathology may represent a fundamental neurobiological substrate for schizophrenia symptoms. Despite the extensive description of dendritic spine pathology in various corticolimbic areas in schizophrenia, its manifestation in the temporal lobe beyond the hippocampus remains underexplored, despite consistent reports of volume loss and gray matter reduction in this region. This study aimed to assess the structural neuroplasticity of pyramidal cells in two temporal lobe regions, namely the primary auditory cortex (Au1) and the entorhinal cortex (Ent), in adult male rats with neonatal ventral hippocampus lesion (NVHL), a widely utilized developmental model of schizophrenia. Rats with NVHL exhibited decreased dendritic spine density in neurons of layers 3 and 5 in both Au1 and Ent, alongside a reduction in mushroom spine population, indicative of synaptic weakening and confirming the presence of dendritic spine pathology in these regions. Notably, previous animal studies have highlighted the ability of atypical antipsychotic drugs to target synapses at both structural and functional levels. Thus, we investigated the effects of two such drugs, olanzapine (OLZ) and risperidone (RISP), on dendritic spine pathology in the temporal lobe cortex. Both OLZ and RISP demonstrated the capacity to increase dendritic spine density and mushroom spine population, thereby ameliorating dendritic spine pathology in Au1 and Ent in rats with NVHL. However, these drugs

exhibited differential effects on the thin spine population associated with spinogenesis and the stubby spine population linked to spine/dendrite calcium dynamics. Our findings provide further support for the proposition that atypical antipsychotics may alleviate schizophrenia symptoms through their neuroplasticity effects at the dendritic spine level, underscoring the potential of these structures as promising targets for drug development beyond the modulation of monoaminergic neurotransmission.

Disclosures: H. Tendilla-Beltrán: None. **D.L. Perez Osornio:** None. **D. Apam-Castillejos:** None. **G. Flores:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.08/X33

Topic: H.13. Schizophrenia

Support: Leon Levy Foundation
NIH Grant 1R25MH125775-01

Title: Probing the Impact of Antipsychotics on Dynamic Microtubules In Neuronal Cultures

Authors: *R. T. DOSUMU-JOHNSON[1], A. COMINCINI[2], E. KANTER[2], F. BARTOLINI[3], D. L. SULZER[2];
[1]Dept. of Psychiatry, Columbia Univ. / New York State Psychiatric Inst., New York, NY; [2]Columbia Univ., New York City, NY; [3]Pathology & Cell Biol., Columbia Med. Ctr., New York, NY

Abstract: Neuronal form and function rely on microtubules, critical cytoskeletal components that convert between stable and dynamic forms. Dynamic instability, characterized by the rapid growth and shrinkage of the dynamic pool, has recently been found to play key roles in synaptic plasticity, affecting both presynaptic and postsynaptic sites. Numerous studies implicate microtubules and microtubule-associated proteins in psychiatric diseases, including schizophrenia, attention deficit hyperactivity disorder, depression, bipolar disorder, and autism spectrum disorder. To explore microtubule dynamics in living neurons, we developed two adeno-associated virus (AAV) constructs expressing a fluorescent microtubule cap protein, EB3, allowing real-time tracking of microtubule dynamics. One construct used a bicistronic element for visualizing cellular architecture and dynamic activity in cortical neuron cultures, while the other employed a Double-Floxed Inverted Open reading frame for cell-type specific expression in midbrain dopaminergic neurons, integrating dynamic microtubule tracking with calcium imaging. Infected neuronal cultures were imaged at baseline and after treatment with haloperidol (0.1 µM), clozapine (1 µM), or vehicle control, using custom ImageJ scripts for analysis. Results indicated that clozapine altered dynamic microtubule instability via enhanced depolymerization, potentially affecting organelle trafficking and synaptic activity. Our approach provides a novel

pathway for investigating microtubule dynamics in neuron subtypes and assessing the impact of antipsychotics on these dynamics. These findings may represent a novel role for clozapine which may contribute to the superior efficacy of clozapine clinically in treatment-refractory schizophrenia and negative symptoms. Future work will adapt this approach to probe microtubule dynamics in models of schizophrenia, autism spectrum disorder, and early life stress.

Disclosures: R.T. Dosumu-Johnson: None. **A. Comincini:** None. **E. Kanter:** None. **F. Bartolini:** None. **D.L. Sulzer:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.09/X34

Topic: H.13. Schizophrenia

Title: Effects of chronic haloperidol treatment in Disc1 heterozygous mutant mice

Authors: *C. WU[1], L.-J. LEE[2];
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Abstract: The heterozygous mutant of Disrupted-in-Schizophrenia 1 (Disc1 Het) had been established as a mouse model of schizophrenia. To model the long-term consequences of antipsychotic treatment in patients with schizophrenia, we administered haloperidol (Halo), a typical antipsychotic, to adult Disc1 Het mice and used wild-type (WT) mice as control. Haloperidol (0.5 mg/kg/day) or vehicle (normal saline) was intraperitoneally injected in mice. On the day of the test, each mouse was placed in the center of an open-field apparatus and a single dose of amphetamine (2.5 mg/kg) was then given. Compared with the vehicle group, haloperidol-treated WT mice exhibited greater locomotor activity, a sign of dopamine supersensitivity. However, in Disc1 Het mice, amphetamine-induced locomotor activities were comparable between haloperidol- and vehicle-treated ones. Our results demonstrated chronic haloperidol-induced *dopamine* supersensitivity in WT but not in Disc1 Het mice. Since haloperidol effectively occupies the dopamine D2 receptor (D2R), the role of D2R and related signaling molecules will be determined in the chronic haloperidol paradigm.

Disclosures: C. Wu: None. **L. Lee:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

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Program #/Poster #: PSTR372.10/X35

Topic: H.13. Schizophrenia

Support: RO1MH110921
RO1 MH075916
P50MH096891

Title: Long-term effects of adolescent risperidone on behavior and prefrontal cortex activity in mice

Authors: *A. D. ALICEA-PAUNETO[1,2], W. ZHANG[1,2], M. MSACKYI[1,2], A. WU[1,2], A. MARC[1,2], C.-G. HAHN[1,2,3], K. BORGMANN-WINTER[1,2,3];
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Abstract: The prescription of antipsychotics for off-label indications during the adolescent period of development has increased significantly over the last decade, particularly among young males. This rise in off-label use raises concerns about potential long-term neurobiological effects, especially considering the understudied impact of these medications on the developing brain. To address this knowledge gap, we investigated the enduring effects of adolescent antipsychotic treatment on behavior and brain activity in mice. Mice received risperidone (4 mg/kg) or saline between P28-49 (21 days), and their behavior and brain activity were evaluated around P62-110. We specifically studied working memory, social memory, anxiety levels, and spatial memory using Y-maze, three-chamber social interaction, open field, and novel object recognition. Our preliminary findings suggest that treatment with risperidone results in a significant increase in thigmotaxis in the open field test, suggesting anxiogenic-like effects persisting into adulthood specifically in female mice. (two-way ANOVA F (3,19) =7.0, p=0.0022, post-hoc Tukey, p=0.0146). To assess the impact of antipsychotics on brain function, we performed vivo Ca2+ imaging using a two-photon microscope focusing on layer two neurons of the M2 cortex as well as Fiber Photometry focusing on the prelimbic prefrontal cortex in awake animals during adulthood. We observed risperidone treatment was associated with reduced neuronal firing frequency in the frontal cortex (one-way ANOVA F= (3, 536) = 16.31, p= P<0.0001). These results underscore the potential for long-lasting negative consequences of adolescent antipsychotic exposure on social behavior and anxiety, highlighting the need for further research to validate and elucidate these findings. This improved understanding can inform decisions regarding the use of antipsychotics during adolescence.

Disclosures: A.D. Alicea-Pauneto: None. **W. Zhang:** None. **M. Msackyi:** None. **A. Wu:** None. **A. Marc:** None. **C. Hahn:** None. **K. Borgmann-Winter:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.11/Y1

Topic: H.13. Schizophrenia

Support: AMED: JP21wm0425007
JSPS: JP23H02669
JSPS: JP23K19425
JSPS: JP24K18365

Title: Rho-kinase 2 is involved in cognitive dysfunction in mouse models of schizophrenia.

Authors: *R. TANAKA[1], J. LIAO[1], W. ZHU[1], K. FUKUZAWA[1], D. MORI[2], A. MOURI[3], T. NAGAI[4], T. NABESHIMA[7], K. KAIBUCHI[5], D. TACHIBANA[8], Y. KOBAYASHI[8], N. OZAKI[2], H. MIZOGUCHI[1], K. YAMADA[1,6];
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Abstract: [Introduction] Rho-kinase is a serine/threonine kinase that regulates actin dynamics. We have previously demonstrated that Rho-kinase inhibitor, fasudil ameliorates cognitive dysfunction in mouse models of schizophrenia, suggesting that Rho-kinase could be a potential therapeutic target for schizophrenia. However, fasudil is known to cause side effect such as hypotension, which may impede its clinical application for schizophrenia. We hypothesized that selective inhibition of Rho-kinase 2, predominantly expressed in the brain, might exhibit antipsychotic-like effects with fewer cardiovascular side effect. Thus, in this study, we evaluated the effect of a selective Rho-kinase 2 inhibitor, belumosudil (KD025), on cognitive dysfunction in mouse models of schizophrenia to investigate Rho-kinase 2 as a potential therapeutic target for schizophrenia. **[Methods]** We utilized several mouse models of schizophrenia, including a genetic model that replicates the gene variants identified in the Japanese schizophrenia patient (*Arhgap10* S490P/NHEJ mice) and pharmacological models induced by either methamphetamine or MK-801. First, we measured the phosphorylation levels of myosin phosphatase-targeting subunit 1 (MYPT1), a substrate of Rho-kinase 2, in the medial prefrontal cortex (mPFC) and the striatum of *Arhgap10* S490P/NHEJ mice and methamphetamine-treated mice 2 h after KD025 (200 mg/kg, p.o.) treatment by immunohistochemistry. Second, we examined the effects of KD025 (50-200 mg/kg, p.o.) on cognitive deficits in *Arhgap10* S490P/NHEJ mice and methamphetamine- or MK-801-treated mice using a touchscreen-based visual discrimination task. Finally, we evaluated whether KD025 (200, 1000 mg/kg, p.o.) did not induce hypotension and typical antipsychotics side effects such as extrapyramidal symptoms and hyperprolactinemia in mice. **[Results & Discussion]** KD025 suppressed the increased phosphorylation levels of MYPT1 in the mPFC of *Arhgap10* S490P/NHEJ mice and in the striatum of methamphetamine-treated mice. Furthermore, KD025 dose-dependently ameliorated cognitive deficits in the visual discrimination task in *Arhgap10* S490P/NHEJ mice and methamphetamine- or MK-801-treated mice. Oral administration of KD025 did not affect systolic blood pressure nor induce extrapyramidal symptoms or hyperprolactinemia in mice.

[Conclusion] These results suggest that Rho-kinase 2 is a potential therapeutic target for cognitive deficits in schizophrenia, without hypotension, extrapyramidal symptoms, or hyperprolactinemia.

Disclosures: R. Tanaka: None. **J. Liao:** None. **W. Zhu:** None. **K. Fukuzawa:** None. **D. Mori:** None. **A. Mouri:** None. **T. Nagai:** None. **T. Nabeshima:** None. **K. Kaibuchi:** None. **D. Tachibana:** A. Employment/Salary (full or part-time):; Sumitomo Pharma Co., Ltd. **Y. Kobayashi:** A. Employment/Salary (full or part-time):; Sumitomo Pharma Co., Ltd.. **N. Ozaki:** None. **H. Mizoguchi:** 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.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Sumitomo Pharma Co., Ltd.. **K. Yamada:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.12/Web Only

Topic: H.13. Schizophrenia

Support: Stanley Foundation

Title: Developing modulators of NR3C2 as a treatment for schizophrenia

Authors: *T. ZHU[1], R. LIN[2], O. GUICHERIT[3], M. H. SHENG[2], M. WEIWER[3], J. Q. PAN[2]; [1]Broad Inst. of MIT and Harvard, Cambridge, MA; [2]Stanley Ctr. for Psychiatric Res., Broad Inst. of MIT and Harvard, Cambridge, MA; [3]Ctr. for Develop. of Therapeut., Broad Inst. of MIT and Harvard, Cambridge, MA

Abstract: Stress affects mental health and is the leading environmental risk factor for schizophrenia (SCZ). Normally, our bodies produce cortisol that follows circadian rhythm for various physiology functions; during stress, the level of cortisol rises sharply for life-preserving responses. However, the level and/or the dynamics of cortisol go awry in SCZ, which indicates altered stress response and may cause maladaptive behaviors. NR3C2 is a druggable nuclear receptor that regulates gene expression in response to mineralocorticoid and glucocorticoid in the brain. Literature findings have shown that inhibition of NR3C2 elevates or prolongs cortisol secretion in human (or corticosterone in rodents), suggesting NR3C2 as a regulator for stress response. Our in-house studies reveal that loss-of-function (LoF) variants of NR3C2 increased risk for SCZ (SCHEMA) and the reduced expression of NR3C2 correlated with altered stress response in Xpo7 LoF mice. Collectively, these findings establish a link between NR3C2 hypofunction and SCZ, and we therefore hypothesize that enhancing NR3C2 function in the brain will restore the aberrant stress response in patients with SCZ. We start this project by examining Nr3c2 LoF mice. This would allow us to understand how LoF of this target affects the

brain and behaviors, and to identify phenotypes that can potentially be restored by NR3C2 agonist. Using bulk RNAseq we found that gene sets from multiple molecular pathways, including those related to synapse, were enriched in brain regions including the prefrontal cortex, dorsal hippocampus, nucleus accumbens and thalamus from Nr3c2 LoF mice. Behaviorally, we found that these animals were hyperactive during wakefulness. To identify chemical matters that can modulate NR3C2 function in vivo, we start with a chemical scaffold that can selectively target NR3C2. After testing over 40 analogs, we identified BRD3173, a selective non-steroidal NR3C2 agonist, in parallel with a selective NR3C2 antagonist BRD3650. Both compounds can enter and remain in the brain for 4h. These tool compounds allow us to further understand the biology of NR3C2 in the brain and to validate the therapeutic hypothesis.

Disclosures: T. Zhu: None. **R. Lin:** None. **O. Guicherit:** None. **M.H. Sheng:** None. **M. Weiwer:** None. **J.Q. Pan:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.13/Y2

Topic: H.13. Schizophrenia

Title: Dynamics of 40 hz click train elicited gamma: the rodent prefrontal cortex imposes a “minimum number of clicks” criterion for phase synchrony

Authors: *D. GAUTAM[1], R. BERGER[2], J. PHAM[2], S. V. DIGAVALLI[3];
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Abstract: Previously, we demonstrated that in the rodent prefrontal cortex (PFC), 40 Hz click train stimuli elicit a robust evoked response that is unsurprisingly coincident with the stimuli. However, when this EEG signal is band-pass filtered (38-42 Hz) to reveal gamma oscillations at ~ 40 Hz, we noted that they appear not time-locked to the stim onset but lagging behind by several hundred milliseconds. Moreover, the gamma oscillations outlast the click trains by ~ 200 ms. This suggests that the narrow band gamma is an induced response, instigated by, but not strictly time-locked to, the 40 Hz train stimuli. It is however unclear if the latency to develop gamma synchrony in the PFC is invariant or is dependent on the number of clicks presented. For example, are two clicks at 40 Hz enough to trigger gamma oscillations? If 2 clicks are not enough, how many are needed before gamma synchrony is triggered? To answer these, we presented 2, 4, 6, 8, 10 and 12 clicks at 40 Hz in a random order to conscious adult SD rats of either sex, implanted with an epidural electrode over the right PFC and referred to a cerebellar lead. While all clicks at 40 Hz elicited a strong evoked response, only 8 clicks and above showed a prominent gamma synchrony. Relative to saline, pretreatment with selective (NR2B; CP101,606, 3 and 10 mpk, sc) and non-selective (MK801; 0.05 mpk, sc) NMDA channel blockers weakened gamma synchrony. To summarize, the rodent prefrontal cortex shows robust

evoked response to click trains at 40 Hz, whether presented as 2 clicks or 12 clicks. However, narrow band gamma synchrony is triggered only when there are at least 8 clicks in a train. We speculate that rapid back-to-back click stimuli are required to activate NMDA receptors in order to induce gamma oscillations. Furthermore, our results reveal for the first time that click-train induced gamma synchrony in the PFC is a non-linear process. It depends on accumulating effects of discrete clicks to reach a response threshold, a process that involves the activation of NR2B-selective as well as NR1 containing NMDA receptors.

Disclosures: D. Gautam: None. **R. Berger:** None. **J. Pham:** None. **S.V. Digavalli:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.14/Web Only

Topic: H.13. Schizophrenia

Title: Schizotypy Correlates with Poor Event Segmentation: Insights for Schizophrenia Spectrum

Authors: *C. KHALIFEH[1], Y. NIV[2], O. BEIN[3];
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Abstract: Schizophrenia is a spectrum of mental disorders that impair individuals' ability to perceive and understand their environment. A critical aspect of understanding our environment is our ability to parse continuous experiences into discrete events in our minds, a process termed ‘event segmentation.’ Understanding segmentation along the spectrum of schizophrenia severity (i.e., schizotypy) and symptoms can facilitate our understanding of the mechanisms underlying disorganized perception in schizophrenia. To that end, online participants (N=483) completed a task in which they segmented short movie clips into discrete units by indicating when in their mind one unit ends and another begins. Participants with higher levels of schizotypy (based on self-report) indicated segments in less typical time points, as reflected by less agreement with the group’s segmentation norm. That is even though they had the same number of segments. These results reflect a disorganized and less structured perception of events in schizotypy. Additionally, symptoms of perceptual dysregulation specifically, more so than eccentricity and unusual beliefs, correlated with poorer segmentation. This study contributes to our understanding of the relationship between schizotypy and perceptual organization, shedding light on potential cognitive mechanisms underlying psychotic experiences.

Disclosures: C. Khalifeh: None. **Y. Niv:** None. **O. Bein:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

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Program #/Poster #: PSTR372.15/Y3

Topic: H.13. Schizophrenia

Support: R01MH110921
R01MH075916
P50MH096891

Title: Altered protein-protein interactions in synaptic microdomains in schizophrenia

Authors: *A. MARC[1,2], W. ZHANG[3,4], M. MSACKYI[3,4], A. ALICEA-PAUNETO[3,4], K. BORGMANN-WINTER[3,5,4], C.-G. HAHN[3,5,4];
[1]Farber Inst. of Neurosci. Thomas Jefferson Univ., Philadelphia, PA; [2]Department of Neuroscience, The Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA; [3]Dept. of Neurosci., The Sidney Kimmel Med. Col. at Thomas Jefferson Univ., Philadelphia, PA; [4]Farber Institute of Neuroscience, Thomas Jefferson University, Philadelphia, PA; [5]Department of Psychiatry and Behavioral Sciences & Neuroscience, The Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA

Abstract: Schizophrenia is a complex trait disorder that is precipitated by combinations of the hundreds of genetic risk variants and their epigenetic modifications. Genome wide association studies have identified the synapse as a locus of pathophysiologic mechanisms of the illness, particularly the glutamatergic synapse. Our group has demonstrated attenuated signaling activity in NMDAR and mGluR5 complexes in human postmortem dorsolateral postmortem prefrontal cortex (DLPFC) of schizophrenia, which were found to result from altered proteins-protein interactions (PPIs) within each complex. To further test where these altered PPIs reside, postsynaptic density (PSD) and presynaptic particle fractions (PPF) from 5 individuals and their age/sex matched controls (n = 10) were fractionated from human postmortem DLPFC and analyzed with the Astral Mass Spectrometer in data independent acquisition (DIA) mode. 9,800 proteins were identified in the PPF and PSD. The PPF contained 181 proteins observed to be enriched by 3-57 fold in comparison to the PSD. The PSD contained 2,500 proteins observed to be enriched by 3-62 fold in comparison to the PPF. Next, we looked to determine the proteins that were differentially represented in SCZ vs. control. Setting an alpha of 0.05 and found 288 proteins that are altered in the PSD of schizophrenia subjects. Of these, 74 proteins were decreased by the range between 7% to 54%, while 214 proteins were increased by up to 2.5 fold. Pathway analyses showed that these proteins were clustered around pathways including the postsynaptic density, glutamatergic synapse, SH3 domain and SH3 binding domain. In the PPF, we found 93 proteins that are altered in schizophrenia subjects. Of these, 57 proteins were decreased by the range between 10% to 68%, while 36 proteins were increased by up to 2.8 fold. These proteins were clustered around pathways including the endocytosis, apical plasma membranes, microtubule associated complexes. Previously, we examined possible PPI alterations in NR1 complexes and mGluR5 complexes using immunoprecipitation - mass spectrometry of DLPFC and found that 20 of 131 proteins identified in NR1 complexes and 18 of 115 proteins identified in mGluR5 complexes were altered in SCZ. According to DIA, Only 2

of the 20 in NR1 complexes and 6 of the 18 in mGluR5 complexes were differentially represented in the PSD. This indicates that altered PPIs may not be explained solely by alterations in protein content in the PSD, but rather variation in binding affinity. Taken together, these findings validate our group's focus on the glutamatergic synapse, and PPIs, as a convergence and intervention point in schizophrenia.

Disclosures: A. Marc: None. **W. Zhang:** None. **M. Msackyi:** None. **A. Alicea-Pauneto:** None. **K. Borgmann-Winter:** None. **C. Hahn:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.16/Y4

Topic: H.13. Schizophrenia

Support: MH132097
MH059852
NIAAA

Title: Directly Converted Induced Neurons Reduced Differentiation Rate in Schizophrenia Patients Compared to Healthy Controls

Authors: *M. MSACKYI[1], J. PREALL[4], W. ZHANG[5,2], A. MARC[2], A. ALICEA-PAUNETO[2], K. BORGMANN-WINTER[2,3], C.-G. HAHN[2,3];
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Abstract: Common neuropsychiatric illnesses are complex trait disorders that involve multitudes of common and rare genetic variants as well as epigenetic factors. For the past decade, iPSC-derived neurons have led the field of in vitro modeling of neuropsychiatric illnesses, which recapitulate the ontogeny of neural cells, offering a powerful paradigm to decipher neurodevelopmental processes. However, iPSC derived neurons may not carry the epigenetic characteristics of donors associated with neuropsychiatric illnesses. However, direct conversion of somatic cells into neurons ($_{DC}$iNs) could offer alternative modeling strategy, while maintaining more epigenetic characteristics of the donors. Olfactory neuroepithelial cells (OEs) are the only readily obtainable neural cells from patients. OEs also retain several neurobiological characteristics of neuropsychiatric illnesses. Previously, Arnold et al have shown that the OE lineage of SCZ patients is altered with a higher density of immature neuronal markers compared to CTRL. Here we report a proof of concept study by characterizing $_{DC}$iN-OE for the rate of neuronal maturation in schizophrenia (SCZ) vs control (CTRL). We compare $_{DC}$iNs from OE ($_{DC}$iN-OE) from 2 subjects with SCZ and their age- sex- matched CTRL cell lines. Live cell images were taken weekly during differentiation and morphological complexity of SCZ vs

CTRL $_{DC}$iN-OEs were assessed using Sholl analysis. Morphologically SCZ-$_{DC}$iN-OE are less complex than CTRL-$_{DC}$iN-OE on day 56 [$p < 0.01$] but this difference was attenuated by day 63 [$p = 0.15$]. ICC analysis was conducted using neural markers MAP2, synapsin 1 and Tuj1 during differentiation at key timepoints. Overall SCZ lines seem to mature more slowly than CTRL lines into $_{DC}$iN-OE with lower percentages of MAP2 and synapsin 1 at day ~50 [$p < 0.05$] however this difference was lost by day ~60 [$p = 0.28$, 0.77 respectively] of differentiation. Finally, multiome analysis was performed at differentiation day 67 for SCZ and CTRL $_{DC}$iN-OEs. Overall results suggest a higher percentage of mature neuronal cells in the CTRL $_{DC}$iN-OE compared to SCZ $_{DC}$iN-OEs which is consistent with our previous findings of altered neuronal lineage in the OE of SCZ compared to controls.

Disclosures: M. Msackyi: None. **J. Preall:** None. **W. Zhang:** None. **A. Marc:** None. **A. Alicea-Pauneto:** None. **K. Borgmann-Winter:** None. **C. Hahn:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR372.17/Y5

Topic: H.13. Schizophrenia

Title: Overconfidence in word recall prediction and its association with psychotic symotins in patients with schizophrenia

Authors: *Y. FLORES MEDINA[1], R. AVILA BRETHERTON[1], J. RAMIREZ-BERMUDEZ[2], M. FLORES-RAMOS[3], R. SARACCO-ALVAREZ[1];
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Abstract: Abstract.
Two cognitive mechanisms have been proposal for the development and maintenance of psychotic symptoms in the patients with chronic psychosis. The first factor a neurocognitive defect leading to an abnormal subjective experience and the second factor is the deficit in the "predictive-coding" mechanism considered a metacognitive function. The aims of this study were 1) assessing the overconfidence in metacognitive judgment in patients with schizophrenia through the prediction of word list recall; 2) to show the association of metacognitive judgment with psychotic symptoms 3) we expect to find a correlation between overconfidence scores with the levels of functionality. **Method.** A total of 51 participants were included. Inclusion criteria: diagnosis of schizophrenia, age of 18 years or more, minimum schooling of six years, under antipsychotic treatment and at least one year with the diagnosis. Participants with delusional disorder, substance induced psychosis, schizoaffective disorder, major neurocognitive disorder and active consumption of any substance other than tobacco were excluded. The subtest of Metamory include in BANFE- 2 was used. PANSS was used to assess the severity of psychiatric

symptoms. The Brief Functioning Assessment Scale was applied for functionality. Descriptive statistics were performed for clinical and sociodemographic data, and a Pearson correlation was used for positive, negative and total or errors in metamemory test, also perseverative and intrusion response with the PANSS subscale scores and FATS score. A multiple linear regression was conducted for predicts the positive symptoms which variables significate related. The strongest correlations are observed between overconfidence errors with positive and excitation symptoms, and PANSS and FAST total scores. A negative correlation was observed between underestimation errors with positive symptoms and overconfidence with negative symptom. The multiple lineal regression model includes the positive and total errors of MC TEST and intrusive response to predict positive symptoms. For the enter model $r=0.78$, $r^2=0.61$; $F=24.57$ and $p< 0.001$. The only predictor variable in the model was the overconfidence errors. Discussion. The data observed during the logistic regression, which show that only metacognitive errors predict positive symptomatology are congruent with the theory of Colheart and Davies (1,3) who state that first factor is not enough for the generation of positive symptoms, but the impairment in the "predictive-coding" mechanism is present in a consistent manner.

Disclosures: Y. Flores Medina: None. **R. Avila Bretherton:** None. **J. Ramirez-Bermudez:** None. **M. Flores-Ramos:** None. **R. Saracco-Alvarez:** None.

Poster

PSTR372: Schizophrenia Therapeutics: Animal and Human Studies

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Program #/Poster #: PSTR372.18/Y6

Topic: H.13. Schizophrenia

Support: Response Pharmaceuticals, Inc.

Title: Inhibition of olanzapine-induced increases in postprandial plasma triglycerides (ppTRIG) and weight gain by an intestinal specific microsomal triglyceride transport protein (iMTP) inhibitor, RDX-002; an exploratory Phase 1b clinical study.

Authors: *J. W. FERKANY[1], W. SASIELA[2], P. SWEETNAM[3], E. KELLER[2], P. SWEETNAM[4];
[1]Develop., [2]Clin., [3]NA, [4]Res., Response Pharmaceuticals, Inc., Falls Church, VA

Abstract: Olanzapine (OLAN) and other atypical antipsychotics (AAPs), while effective for treating schizophrenia and bipolar disorders, are linked to rapid weight gain (AIWG) and increased metabolic risk (MR). Side effects, including hyperlipidemia, hyperglycemia, diabetes, and cardiovascular disease, can negatively impact treatment decisions and patient compliance. A well-tolerated treatment specifically targeting AIWG and MR is urgently needed. The mechanics of AIWG and MR include peripheral and central components. AAPs influence eating behaviors, including increased appetite and caloric intake and changes in food preferences favoring fats and carbohydrates, all of which contribute to acute and chronic AIWG and increase MR in patients.

AAPs have been shown to activate the pregnane X receptor (PXR) in the small intestine. This activation has been linked to the increased expression of intestinal microsomal triglyceride transfer protein (iMTP), a central mediator for the absorption of dietary triglycerides (TRIG) and cholesterols (CH) from the gut. The confluence of AAPs/PXR/iMTP suggested an iMTP inhibitor as a targeted approach to treat AIWG and MR. In this Phase1b study, 24 healthy volunteers received OLAN for seven days, followed by either OLAN alone or OLAN with RDX-002 for another seven days. Compared to baseline (Day 1), OLAN alone significantly increased (54.9%) ppTRIG area under the curve (AUC) by Day 8 ($p=0.009$), and this elevation persisted at Day 15. Importantly, co-administration of RDX-002 with OLAN for seven days significantly reduced ppTRIG by 81.5% ($p<0.001$). Body weight gain from Day 8 to Day 15 was also significantly blunted in the OLAN plus RDX-002 group (mean change 0.49%, $p=0.443$) compared to OLAN alone (mean change 2.21%, $p=0.016$). Additionally, OLAN treatment led to statistically significant increases in LDL-C (25.8%; $p=0.016$)), total cholesterol (16.5%; $p=0.031$)), and non-HDL-C levels (23.6%; $p=0.016$)), which were all prevented by co-administration with RDX-002. This study provides the first clinical evidence supporting the role of iMTP in AIWG. RDX-002 effectively reduced ppTRIGs and blunted body weight gain in OLAN-treated subjects, suggesting its potential to prevent AIWG. As in prior studies, RDX-002 was well-tolerated. These findings highlight the potential of targeting iMTP activity as a therapeutic strategy to manage AAP-induced increases in fat absorption and subsequent weight gain. The data support a potential role for RDX-002, a novel enterocyte-selective small molecule with a defined molecular mechanism and, importantly, no CNS activity, as an adjunct to AAP treatment to prevent AIWG and associated MR.

Disclosures: J.W. Ferkany: A. Employment/Salary (full or part-time):; Response Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Response Pharmaceuticals, Inc. **W. Sasiela:** A. Employment/Salary (full or part-time):; Response Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Response Pharmaceuticals, Inc. **P. Sweetnam:** F. Consulting Fees (e.g., advisory boards); Response Pharmaceuticals, Inc. **E. Keller:** A. Employment/Salary (full or part-time):; Response Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Response Pharmaceuticals, Inc. **P. Sweetnam:** A. Employment/Salary (full or part-time):; Response Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Response Pharmaceuticals, Inc..

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.01/Y7

Topic: I.02. Systems Biology and Bioinformatics

Support: R00MH117393-05

Title: Comprehensive network modeling approaches unravel dynamic enhancer-promoter interactions across neural differentiation

Authors: *W. B. DEGROAT, A. KREIMER;
Ctr. for Advanced Biotech. and Med., Rutgers, The State Univ. of New Jersey, Piscataway, NJ

Abstract: Increasing evidence suggests that a substantial proportion of disease-associated mutations occur in enhancers, regions of non-coding DNA essential to gene regulation. Understanding the architecture and mechanisms of regulatory programs this variation affects can shed light on the apparatuses of human disease.
We collected epigenetic and gene expression datasets from seven early time points during the differentiation of human embryonic stem cells to neural progenitor cells. Focusing on this model system, we constructed intricate networks of enhancer-promoter interactions (E-P-Is), each at a distinct stage of neural induction. These networks functioned as the base of a rich series of analyses, through which we demonstrated their temporal dynamics and enrichment for various neuropsychiatric and neurodevelopmental disorder-associated variants. We applied a Girvan-Newman clustering approach, taking advantage of our network's high modularity, to reveal biologically relevant substructures of regulation with important implications for human health. Additionally, we validated specific E-P-I predictions with transcription factor overexpression and massively parallel reporter assays.
Our findings suggest a comprehensive framework for exploring gene regulation programs and their dynamics across developmental processes, including a rigorous approach to studying the effects of disease-associated variation on transcriptional networks. Our approach is generalizable and can be utilized across different cellular contexts and disorders.

Disclosures: W.B. DeGroat: None. **A. Kreimer:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

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Program #/Poster #: PSTR373.02/Y8

Topic: I.02. Systems Biology and Bioinformatics

Support: NIMH Grant R00MH11739305
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Simons Foundation Grant 1012863NY

Title: Network analysis of enhancer-promoter interactions highlights cell-type specific mechanisms of transcriptional regulation variation

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Abstract: Gene expression, a fundamental determinant of cellular diversity in multicellular organisms, is orchestrated by a complex array of gene regulatory elements that govern transcription in a cell-type-specific manner. Additionally, the vast majority of potential disease associated variants fall into non-coding regions of the DNA and within these elements. Though previously studied, the ability to utilize these regulatory regions to identify disrupting variants remains largely elusive, partially due to regulatory elements variability across cell-types and conditions. To identify important factors within these regions, we generated enhancer-promoter interaction (EPI) networks and investigated the presence of disease associated variants that fall within these regions. Our study analyzed EPI networks for six different neuronal cell types across neural differentiation, allowing us to examine more closely related cell types and across differentiation stages. Our results highlight enhancers as the leading factor of cell type specificity of EPIs, coinciding with previous studies. Additionally, we observe that target genes regulated by cell-type specific enhancers are enriched for cell-type relevant biological processes. Moreover, we find that transcription factor binding sites are less indicative of specific cell types, but rather of cell differentiation stage. Notably, we find that both enhancer and promoter regions within EPI networks can be utilized to identify enrichment of variants associated with neuropsychiatric disorders within specific cell types and network sub-structures. This enrichment within sub-structures can allow for a better understanding of potential mechanisms by which variants may disrupt transcription. Together, our findings suggest that EPIs can be leveraged to better understand cell-type specific regulatory architecture and used as a selection method for disease-associated variants to be tested in future functional assays.

Disclosures: J. Koesterich: None. **S. Williams:** None. **A. Kreimer:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.03/Y9

Topic: I.02. Systems Biology and Bioinformatics

Support: NSF Grant 2046550

Title: Using relative evolutionary rates and enhancer genetic variation across mammals to understand phenotypic diversity of pair bonding

Authors: *R. GANESAN[1], R. REDLICH[2], A. KOWALCZYK[2], H. SESTILI[2], A. WANG[3], A. R. PFENNING[4];
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Abstract: Comparative genomics aims to link molecular changes with phenotypic evolution across a species' evolutionary history. Here, we use genomes from across the mammalian tree to study pair bonding, an evolved trait characterized by long-term, preferential mating episodes between two individuals within the same species. We obtained pair bonding phenotype annotations (Lucas, Clutton-Brock, 2013), and used a phylogeny of 173 mammals constructed from genomes from the Zoonomia Consortium to run an RERconverge analysis on a binary encoding of the pair bonding phenotype, with 24 contemporary socially monogamous mammals and 149 non-pair bonding mammals across multiple clades. We performed ancestral reconstruction using the maximum likelihood inference methods included in the RERconverge categorical expansion. We inferred 11 independent transitions to pair bonding from non-pair bonding ancestral mammals, and performed permulations (phylogeny-informed permutations related to the pair bonding trait) for both the gene correlation results and the biological pathway enrichment results. Clustering on the enriched pathways with the mouse genome informatics (MGI) annotations (Liberzon et al. 2011; Subramanian et al. 2005) notably identified clusters relating to male germ cells, ovarian follicles, the pituitary and luteinizing hormone, and drug response. These highlight important changes occurring during the convergent evolution of pair bonding, many of which are supported by experimental results in pair bonding species including changes due to lower sperm competition, hormones involved in female reproduction, and potential parallels between neural regions involved in drug responses and partner selection. Our compelling pathway enrichment results are evidence that the association of protein coding regions with the evolution of pair bonding captures true signals within the data. We then employed the same alignments to train TACIT (Enhancer-Phenotype Association from Tissue-Aware Conservation Inference Toolkit) models, which uses predicted enhancer activity conservation to connect genetic sequence differences between species to phenotypes across large numbers of mammals. This includes using the sequences underlying open and closed chromatin regions within the Zoonomia phylogenies to train a machine learning model for predicting tissue-specific open chromatin, and associating open chromatin predictions across dozens of mammals with the trait using phyloglm. We can use these results to then make sense of how conservation of, or changes in, subtle genome patterns can help explain the trait evolution.

Disclosures: R. Ganesan: None. **R. Redlich:** None. **A. Kowalczyk:** None. **H. Sestili:** None. **A. Wang:** None. **A.R. Pfenning:** A. Employment/Salary (full or part-time):; Founder of Snail Biosciences. F. Consulting Fees (e.g., advisory boards); Scientific Advisory Board of Avista Therapeutics.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.04/Y10

Topic: I.02. Systems Biology and Bioinformatics

Title: Deciphering non-coding neuropsychiatric variation in the context of gene regulatory networks using massively parallel reporter assays and computational genomics

Authors: *A. KREIMER[1], W. DEGROAT[2];
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Abstract: Enhancers are cis-regulatory elements, non-coding sequences of the DNA that are pivotal to cell type-specific gene regulation. While a consensus that enhancers are hubs for variants that influence human disease has been reached, little is known about how these elements mediate their effects on gene expression. Additionally, the map of these enhancers' location and their target genes is still partial. Computational models, which extrapolate epigenetic markers to regulatory activity, have proven immensely successful in predicting enhancer-promoter interactions (E-P-Is) in recent years. Still, there is room for improvements in these models' ability to capture cell type specificity and more accurately predict E-P-Is.
Massively parallel reporter assays (MPRAs) are a cutting-edge technique for assessing the functionality of regulatory elements and their perturbations under varied conditions (e.g., cell types). Yet, computational methods for analyzing MPRA data in a cell-type-specific manner are still lacking. We utilized MPRA datasets to score and define enhancer regions using sequence-based deep learning models. MPRA offers a single, comparable means of computing the regulatory activity of enhancers across E-P-I networks. Using the well-studied K-562 cell line as a model system, we generated E-P-I networks using our model and other commonly cited approaches; benchmarking was performed by linking enhancers with CRISPR-validated target genes and examining overlaps with expression quantitative trait loci. Overall, we saw improvements in our model's ability to predict cell type-specific E-P-Is compared to existing approaches.
With this novel approach, we created a catalog of E-P-I networks for neural stem cells and neural progenitor cells utilizing a standardized format that enables investigations into disease-associated variation across multiple neuropsychiatric disorders, transcription factor binding, and regulatory substructures.

Disclosures: A. Kreimer: None. **W. DeGroat:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.05/Y11

Topic: I.02. Systems Biology and Bioinformatics

Title: Decoding autism regulatory variants using computational genomics in human iPSC-derived neurons

Authors: *J. LIU[1], J. H. MILLONIG[2], A. KREIMER[3];
[1]Rutgers Univ., Avenel, NJ; [2]Neurosci. and Cell Biol., Rutgers Univ., Piscataway, NJ; [3]Rutgers The State Univ. of New Jersey, Piscataway,NJ, NJ

Abstract: Autism Spectrum Disorder (ASD) is characterized by impaired social and communication skills, along with repetitive and restrictive behavior. ASD affects approximately 2% of the population and is prevalent across racial and ethnic groups. With over 18% of U.S. disability-adjusted life years (DALYs) attributed to mental, behavioral, and neurological disorders, ASD imposes a significant socioeconomic burden, affecting the health, learning, and working capabilities of those involved.
Over the past decade, numerous genome-wide association (GWAS) and whole genome sequencing (WGS) studies have identified thousands of significant autism variants, predominantly in non-coding regions of the genome. These variants are thought to contribute to ASD risk by altering gene expression during neuronal development. Identifying which non-coding variants are functional has been challenging, but is crucial for understanding ASD and discovering new therapeutics.
This proposal aims to use new molecular and computational approaches to determine which cis-regulatory autism variants are functional and how they contribute to disease risk. By leveraging advances in computational modeling and a new high-throughput screening technique called Massively Parallel Reporter Assays (MPRAs), the research will explore omics data from multiple assays (ATAC-seq, ChIP-seq, RNA-seq). This will allow for high-confidence prediction of enhancers and testing of thousands of cis-regulatory variants simultaneously in human iPSC-derived neural progenitor cells (NPCs) and induced neurons (iNs), which are cell types consistently associated with autism risk.
The hypothesis that ASD variants mapping to enhancers are functional and affect gene expression during neurodevelopment will be tested through two aims:1. Mapping noncoding ASD variants to computationally predicted enhancers and ranking them for possible functional effects.2. Testing the functionality of ASD non-coding variants and compiling a comprehensive catalog of functional variants across human neural differentiation.
Upon completion, the research team will identify which common and rare autism variants are functional and develop a computational model to predict how these variants affect gene regulation during neurodevelopment. This will address a significant knowledge gap in autism biology, enhance our understanding of how cis-regulatory variation contributes to ASD etiology, and help define target genes for therapeutic intervention.

Disclosures: J. Liu: None. **J.H. Millonig:** None. **A. Kreimer:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.06/Y12

Topic: I.02. Systems Biology and Bioinformatics

Support: the Grant-in-Aid for JSPS Fellows JP23KJ1789
Saitama Prefectural University Research（SPUR) Grant

Title: Network-based global analysis of the cellular senescence process and senescence phenotype in the peripheral sensory neurons of the dorsal root ganglia

Authors: *S. KAWABATA[1], H. IIJIMA[2], N. KANEMURA[3], K. MURATA[3];
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Abstract: Accumulation of senescent neurons in the dorsal root ganglion (DRG) is an important tissue phenotype that causes age-related degeneration of peripheral sensory nerves. Senescent neurons represent neurons that have undergone cellular senescence, have arrested the cell cycle, but remain in the tissue and play variety of biological role that cause aging. To understand the accumulation of senescent neurons in the DRG during aging, we aimed to elucidate the mechanism that induce cellular senescence in DRG neurons and the role of senescent DRG neurons.We searched the public database GEO using keywords related to “aging”, “DRG” and “Sciatic nerve”. We comprehensively extracted transcriptome datasets that were compared by age and targeted to DRG or sciatic nerve. We defined the senescence level of each dataset based on the expression level of genes encoding cellular senescence factors (p16, p21, and p53), and then moved on to network medicine-based bioinformatics analysis. Specifically, we identified a group of senescence-inducing genes that induce cellular senescence in DRG neurons and genes that characterize senescent neurons by analyzing a protein-protein interaction (PPI) constructed by differentially expressed genes (DEGs) and WGCNA using the top 3000 genes with mean absolute deviation. In addition, we investigated biological pathways associated with aging using gene set enrichment analysis (GSEA) and evaluated their relationship to each group by network propagation based on the random-walk with restart algorithm (RWR).Network medicine-based bioinformatics analysis revealed that age-related Mapk3 decline leads to impaired cholesterol metabolism and biosynthetic function in axons, resulting in compensatory upregulation of Srebf1, a transcription factor involved in lipid and cholesterol metabolism, which in turn leads to CDKN2A-mediated cellular senescence. Furthermore, this analysis revealed that the senescent DRG neurons develop an senescence phenotype characterized by activation of antigen-presenting cells via upregulation of protease Ctss as a hub gene.These molecular mechanisms have been rigorously inferred from network analyses using transcriptomic data, and their validation by in vivo and in vitro experiments in future research will provide a foundation for understanding peripheral sensory neuron aging.

Disclosures: S. Kawabata: None. **H. Iijima:** None. **N. Kanemura:** None. **K. Murata:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.07/Y13

Topic: I.02. Systems Biology and Bioinformatics

Support: 4R00NS119784

Title: Convolutional neural network models of chromatin accessibility reveal base pair-resolution regulatory sequence syntax in the mammalian brain

Authors: *X. LUO[1], S. WANG[2], S. KIM[3], J. SHI[4], S. KUNDU[5], J. SCHREIBER[6], Y. ZHANG[7,8], R. SINHA[9], S. NAIR[9], A. KUNDAJE[10], L. TAN[1], R. CHEN[11];
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Abstract: The sequence basis of gene regulation in mammalian brains remains poorly understood despite recent advances in whole-brain single-cell transcriptomic atlases. Single-nucleus ATAC seq (snATAC-seq) provides chromatin accessibility information at the single-nucleus level and a genome-scale view of potential non-coding regulatory elements. However, it is challenging to decipher the sequence syntax that regulates chromatin accessibility at individual elements across diverse cell types. Here we use a convolutional neural network called ChromBPNet to model DNA sequence features that drive base-resolution chromatin accessibility profiles at 1 million unique regulatory elements from 262 diverse cell types derived from 2.3 million nuclei across the whole mouse brain (data generated by Zu et al., 2023). We used a suite of model interpretation approaches to infer predictive sequence features in each regulatory element and consolidate these patterns into predictive motifs. We identified a vast repertoire of cell-type-specific transcription factor motifs related to brain cell developmental origin and function with dynamic predictive activity across the cell types. We used the models to obtain detailed cell-type specific sequence syntax annotation of all regulatory elements. This demonstrates the utility of chromBPNet in interpreting the regulatory syntax of many closely related brain cell types. We envision that this approach will be of interest for further studies of the gene-regulatory basis of brain cell diversity and function.

Disclosures: X. Luo: None. **S. Wang:** None. **S. Kim:** None. **J. Shi:** None. **S. Kundu:** None. **J. Schreiber:** None. **Y. Zhang:** None. **R. Sinha:** None. **S. Nair:** None. **A. Kundaje:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); DeepGenomics, Immunai, Freenome. F. Consulting Fees (e.g., advisory boards); SerImmune, OpenTargets, TensorBio, Arcardia Science, Illumina (former), PatchBio (former). **L. Tan:** None. **R. Chen:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

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Program #/Poster #: PSTR373.08/Y14

Topic: I.02. Systems Biology and Bioinformatics

Support: IBACS
NCI Grant K25CA270079
NSF 2212512

Title: Identifying the cellular composition of the Inferior Colliculus following noise-induced hearing loss using single cell omics

Authors: *M. R. MOUSSA[1], S. KAPOOR[1], E. FABRIZIO-STOVER[2], J. ZHOU[3,4], A. L. BURGHARD[5];
[1]Univ. of Oklahoma, Norman, OK; [2]Otolarynology, Med. Univ. of South Carolina Neurosci., Charleston, SC; [3]Univ. of Connecticut Hlth. Ctr., Farmington, CT; [4]Yale Univ., New Haven, CT; [5]Neurosci., Univ. of Connecticut Sch. of Med., Farmington, CT

Abstract: Located in the midbrain, the inferior colliculus (IC) is a major hub in the central auditory system. Changes of activity in the IC are implicated in tinnitus, speech processing difficulties, as well as temporal processing deficits. While several different neuron types in the IC have been identified using various approaches such as morphology, histochemistry or electrophysiology, an un-biased approach that encompasses all cell types (including non-neuronal) at once is still missing. In this project, we sequenced 72081 single nuclei RNA (snRNAseq) from the left and right ICs of adult male and female CBA/CaJ mice after bilateral noise exposure (116 dB SPL, 2kHz wide, centered at 16 kHz) and from age and sex matched controls (n=8 per group). Results for the sound exposure group show an expected permanent threshold shift. We identify the cellular composition of both the neuronal and non-neuronal cell populations in the IC and elucidate differential transcriptomic expressions in neuronal phenotypes. Our results highlight enrichment in gene programs implicated in regulation of the apoptotic process and programmed cell death in the sound exposed GABAergic compartment, including Slc15a2 and Il31ra. Our work establishes for the first time the baseline cellular and molecular profiles of the cell groups present in the IC of the adult mouse with normal hearing and after noise-induced hearing loss (NIHL).

Disclosures: M.R. Moussa: None. **S. Kapoor:** None. **E. Fabrizio-Stover:** None. **J. Zhou:** None. **A.L. Burghard:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

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Program #/Poster #: PSTR373.09/Y15

Topic: I.02. Systems Biology and Bioinformatics

Support: National Key R&D Program of China 2021YFA0805100

Title: Reconstructing the Evolution of the Mammalian and Avian Telencephalon through Spatial Molecular Architecture

Authors: *S. LIU;
BGI Res., Hangzhou, China

Abstract: The evolution of amniotes introduced the emergence of intricate brain organization, particularly in the telencephalon, but its genoarchitectonic identity and evolutionary trajectory remain unclear. By constructing spatial transcriptomic atlases of telencephalon across species, we enable comparisons among sauropsids (reptiles and birds), amphibians (axolotls), and mammals (mice and macaques), allowing us to decode the evolutionary relationship between the sauropsid dorsal ventricular ridge and mammalian neocortex. We uncovered two divergent gene regulatory models driving the evolution of the amniote telencephalon: the 'coupled model', characterized by a conserved regulatory relationship between transcription factors (TFs) and effector genes across species, and the 'shift model', where this regulatory relationship varies across species. Notably, we revealed the molecular mechanism behind the functional convergent evolution of the avian DVR and mammalian neocortex, recruiting the same effector genes through divergent TFs. Collectively, our findings shed light on the nuanced evolutionary relationships within the amniote telencephalon, providing a new fundamental understanding of brain evolution.

Disclosures: S. Liu: None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

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Program #/Poster #: PSTR373.10/Web Only

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant P30 DA018310
USDA Grant 2022 3842038610

Title: Cell-dependent variation on cell adhesion molecule profiles characterized by single-nucleus RNA-sequencing

Authors: *B. SOUTHEY[1], G. SUNDERLAND[2], S. RODRIGUEZ ZAS[1];
[1]Univ. of Illinois at Urbana-Champaign, Urbana, IL; [2]Univ. of Illinois Urbana-Champaign, Urbana, IL

Abstract: The many cell types that are present in the amygdala play different roles in modulating memory, emotions, and decision-making processes. Likewise, the molecular mechanisms in neurons, glial cells, and other cell types contribute differently to the plasticity of the amygdala to external factors such as drugs of abuse, which in turn impact physiology and behavior. Among these molecular processes, cell adhesion molecules mediate interactions

between neurons and the extracellular environment and regulation of excitatory synaptic transmission and plasticity. The objectives of this study are to characterize the cell types in the amygdala of a rat model of cocaine addiction using single-nucleus RNA sequencing and to explore profiles of cell adhesion molecules in reward dependency across cell types. The amygdala of six male rats that self-administered cocaine and six male rats serving as controls were profiled. Single-nucleus RNA sequencing libraries were obtained from the individual samples, and approximately 12,000 nuclei were sequenced. Data preprocessing, normalization, sample integration, and differential expression were accomplished using the software Seurat. The distribution of cells was depicted in two dimensions using the uniform manifold approximation and projection, and cell types were identified using gene markers. This analysis enabled the identification of cell types, including glutamatergic neurons, microglia, and astrocytes, using markers including Adcyap1, Tmem119, and Gfap. The enriched Kyoto of Encyclopedia of Genes and Gene pathways among genes differentially expressed between treatment groups within a cell type, including the cocaine addiction pathway and cell adhesion molecules. The clustering of cells based on cell adhesion molecule profiles offered a complementary perspective into the potential distinct impact of cocaine. The present analysis at the single-cell level further the characterization of the manner in which different amygdala cell types respond to psychoactive substances.

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Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

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Program #/Poster #: PSTR373.11/Y16

Topic: I.02. Systems Biology and Bioinformatics

Title: Analysis of microexon alternative splicing patterns in neural-differential regulated genes across mouse developmental stages

Authors: *J. KIM;
Korea Inst. of Sci. and Technol. Information, Daejeon, Korea, Republic of

Abstract: Microexons, short exon sequences ranging from 3 to 27 base pairs, are pivotal in neurological disorders and neuron-specific gene expression. Mainly detected in neurons, microexons show altered alternative splicing patterns in genes linked to neurological abnormalities, suggesting their role in regulating neural development and synaptic function. Neural-differential regulated exons exhibit varying Percent Spliced In (PSI) patterns between neuronal and non-neuronal cells, as evidenced by changes in PSI of neural-differential regulated microexons in postmortem brain RNA-seq of autism patients. We analyzed whole cortex RNA-seq data from mice across nine developmental stages: embryonic (Embryo 14.5, 16.5), postnatal (P0, P4, P7, P15, P30, P110), and 21 months. Our findings reveal stage-specific patterns for microexons in genes like Arhgap44, Ash2l, Cd99I2, Dnajc13, Myh9, and Shank3, with PSI

increasing as development progresses, while genes like Bin1, Ckap5, Dip2a, Plch2, and Sh3glb1 exhibit decreasing PSI. This underscores the dynamic regulation of microexon splicing during mouse cortex development. Genes with increasing PSI suggest roles in neural maturation and synaptic function, while those with decreasing PSI may be involved in other cellular processes or developmental transitions. These findings emphasize the importance of studying microexon dynamics in understanding neurodevelopment and associated disorders.

Disclosures: J. Kim: None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

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Program #/Poster #: PSTR373.12/Y17

Topic: I.02. Systems Biology and Bioinformatics

Support: NINDS R21NS121589

Title: Deciphering transcriptomic profiles of peripheral blood mononuclear cells in moyamoya disease using single-cell RNAseq

Authors: *Z. DEMIRAG, H. UCHINO, K. TOKAIRIN, S. P. RAO, T. C. CHIANG, G. MORTON, A. G. LEE, M. Y. CHENG, G. K. STEINBERG;
Dept. of Neurosurg. and Stanford Stroke Ctr., Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Moyamoya Disease (MMD) is a complex cerebrovascular disease marked by progressive idiopathic steno-occlusive changes in the cerebral arteries. Previous studies have suggested that dysregulated genes in the peripheral blood of MMD patients are involved in extracellular matrix organization, as well as immune and inflammatory responses. However, the mechanism by which the immune response contributes to the progression of MMD is not clear. To address this, we investigated the immune landscape and the cellular heterogeneity in the peripheral blood mononuclear cells (PBMCs) of MMD patients using single-cell RNA sequencing (scRNA-seq).
Peripheral venous blood samples were collected from 3 bilateral MMD patients, 2 non-MMD patients (aneurysm or cavernous malformation) and 2 healthy controls. PBMCs were isolated and processed for single-cell RNA sequencing. Immune cell heterogeneity and differentially expressed genes (DEGs) in each cell type were identified. Top biological functions and canonical pathways were determined using Ingenuity Pathway Analysis (IPA). Flow cytometry was used to validate key immune populations and fluorescence-activated cell sorting (FACS) was used to isolate specific immune populations for transcriptome analysis.
Preliminary analysis showed proportional differences across distinct cell types between MMD and healthy controls, including CD8+ NKT, Naïve CD8+ T, CD4+ NKT, Naïve B cells and non-classical monocytes. Analysis of the DEGs showed high transcriptomic changes in CD8+ NKT, CD4+ NKT and classical monocytes. Biological function and pathway analysis revealed

predicted activation in RNA and protein metabolism in all 3 cell types. Notably, classical monocytes exhibit predicted activation in oxidative stress, response to hypoxia and neutrophil signaling. Naïve CD4+ T cells and CD8+ NKT cells exhibit predicted inhibition in mTOR signaling, T cell receptor and interleukin signaling and cell surface interactions at vascular wall. Our study revealed unique transcriptomic signatures of immune cells in MMD and highlighted key immune cell types that may contribute to its pathogenesis. Ongoing studies utilize FACS and RNA sequencing to validate these specific immune populations and their transcriptomes in a larger cohort. These findings indicate a significant role of peripheral immune cells in MMD.

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Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

Support: NIH R21HG011506
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NIH R21CA264637
DoD W81XWH-21-1-0805
NIH K01CA229995

Title: Tracing regulatory element networks using epigenetic traits to identify key transcription factors

Authors: D. MULLEN, Z. WU, E. NELSON-MOORE, H. CAO, L. HAN, I. OFFRINGA, ***S. K. RHIE**;
Biochem. and Mol. Med., USC, Los Angeles, CA

Abstract: There is a lack of publicly available bioinformatic tools that can be widely used by researchers to identify transcription factors (TFs) that regulate cell type-specific regulatory elements (REs). To address this, we expanded on our previous bioinformatic frameworks and developed the tracing regulatory element networks using epigenetic traits (TENET) R/Bioconductor package. The TENET Bioconductor package utilizes histone mark and open chromatin datasets, along with matched DNA methylation and gene expression data to identify dysregulated REs and the TFs bound to them in a particular cell or tissue type in comparison to another. To assist in identifying TFs and REs linked to a particular cell type, we collected hundreds of epigenomic datasets from a variety of cell lines, primary cells, and tissues. Moreover, we developed methods to interrogate findings with motif databases, clinical information, and other genomic and chromatin conformation capture datasets. Furthermore, we

applied our developed framework to publicly available epigenomic datasets and demonstrated its applicability, highlighting TFs and REs linked to different cell types. Our approach enables researchers to better characterize the epigenomes of cell types of interest for future clinical application by identifying key TFs and REs.

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Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

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HI21C1705
HI22C0782

Title: The use of ERASURE to overcome antibody cross-talk and high autofluorescence in ultra-multiplexed imaging

Authors: W. LA[1], S. BAE[2], J. SEO[3], H. KIM[4], J. CHO[2], H. NAM[2], S. HAN[2], E. KIM[2], Y. YOON[2], ***J.-B. CHANG**[1];
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Abstract: Spatial proteomics is a highly attractive method for investigating the 3D organization of cells and microenvironments in various tissues, and multiplexed fluorescence imaging has been an efficient tool in this field. However, available antibodies are mostly developed for only a few host species, and the high level of autofluorescence in tissues like FFPE samples hinders the effective design of multiplexed imaging experiments. Current solutions to this problem involve the application of specific chemicals or multiple imaging rounds, which limits further applications. Here, we introduce ERASURE, which addresses both the limited availability of antibody host species and the high level of autofluorescence. ERASURE enables the use of antibodies from the same host species, as well as multiplexed imaging in specimens with a high level of autofluorescence. ERASURE can be a useful tool that allows the use of conventional

reagents, antibodies, and experimental procedures regardless of the host species and enables the imaging of samples with high autofluorescence.

Disclosures: W. La: None. **S. Bae:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KAIST. **J. Seo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KAIST. **H. Kim:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KAIST. **J. Cho:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KAIST. **H. Nam:** None. **S. Han:** None. **E. Kim:** None. **Y. Yoon:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KAIST. **J. Chang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KAIST.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.15/Y20

Topic: I.02. Systems Biology and Bioinformatics

Title: In situ proximity ligation assays possess an untapped potential for protein-protein interaction studies in the central nervous system

Authors: *S. E. BODBIN, D. RAYKOVA, A. ZIEBA WICHER;
Navinci Diagnostics, Uppsala, Sweden

Abstract: Introduction Immune checkpoints (ICs), such as the PD-1/PD-L1 axis, are inhibitory signaling pathways that down-regulate the immune responses of T cells and play a crucial role in maintaining immune self-tolerance in peripheral tissues. Microglia are the innate immune cells of the central nervous system (CNS) with the role of maintaining the tissue and responding to infections or injury. Many diseases of the CNS arise due to the suppression of the CNS immune response resulting from PD1 signaling of microglia and infiltrating peripheral immune cells. Under normal conditions, microglia expression of PD1 is low, however under pathological conditions, it increases. Using Navinci's sensitive and specific *in situ* proximity ligation technology combined with additional biomarker staining, it was possible to visualize the immune landscape in the context of the PD1/PD-L1 axis in CNS pathologies. **M&M** The Naveni® PD1/PD-L1 Atto647N kit was used for the detection of the PD-1/PD-L1 protein-protein interaction. To visualize the interaction, formalin-fixed, paraffin-embedded tissue slides and tumor tissue microarrays were incubated with monoclonal antibodies specific to each of the target proteins. Following this, the slides were incubated with Navenibodies, secondary antibodies conjugated to proprietary oligo arms. When these are in proximity of 40 nm or less, an amplified signal is created, representing the protein-protein interaction. This signal was detected

using a fluorescent readout. To add the spatial context of the tumor microenvironment (TME), additional immunofluorescent staining of CD4, TMEM119 and Iba1 were added during the detection step of the *in situ* proximity ligation assay. **Results** PD1/PD-L1 interactions were assessed using the Naveni® proximity ligation technology in CNS pathological and healthy tissues. Increased PD1/PD-L1 signaling was observed in cerebrum samples of glioblastoma, T cell lymphoma and glioma sarcomatosum, compared to healthy cerebrum tissue. The additional costaining with immune cell and prognostic markers enabled the visualization of the TME and microglia and their involvement in the IC interaction. **Conclusions** This study demonstrates the potential that *in situ* proximity ligation assays possess in investigating protein-protein interactions in CNS pathologies. The implication of PD1 in CNS disorders and the therapeutic relevance of the PD1/PD-L1 IC denotes the importance of studying the interaction and the surrounding immune landscape. Such studies could aid in the development of treatments for a vast array of pathologies, and in understanding neuromodulation.

Disclosures: S.E. Bodbin: A. Employment/Salary (full or part-time):; Navinci Diagnostics AB. **D. Raykova:** A. Employment/Salary (full or part-time):; Navinci Diagnostics. **A. Zieba Wicher:** A. Employment/Salary (full or part-time):; Navinci Diagnostics.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.16/Y21

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH/NIMH U01MH122592
NIH/NIMH U01MH122591
NIH/NIMH U01MH122590

Title: The dynamic cycle of neuronal DNA (hydroxy)methyl-cytosine across the human lifespan

Authors: *H. XU[1], J.-F. CHIEN[1], J. LI[2], R. VADUKAPURAM[3], A. KOZLENKOV[4], Y. WEI[5], C. LIU[5], S. DRACHEVA[4], E. A. MUKAMEL[2];
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Abstract: DNA methylation is a critical epigenetic modification in neurons, essential for establishing the identity of neuronal cell types, shaping genome structure, and modulating gene expression. Although the vast majority of cytosines at CG sites are methylated in neurons at birth, a significant portion are subsequently transformed into hydroxymethylcytosine (hmC) via TET enzymes. Further oxidation of hmC has been proposed to facilitate subsequent demethylation via several pathways. Although these pathways are known, data on the dynamics of cytosine modifications in human neurons and their specific subtypes throughout the lifespan

remains limited.
To address this knowledge gap, we analyzed genome-wide methylcytosine (mC) and hydroxymethylcytosine (hmC) levels in GABAergic and glutamatergic neurons sorted from the prefrontal cortex of 99 human donors aged 0 to 77. We performed bisulfite and oxidative bisulfite whole genome sequencing to estimate total methylation (mC + hmC) and methylation (mC), respectively. Throughout the genome, ~32-38% of mC was converted to hmC, primarily during the first decade of life. We developed a dynamical system model to estimate the rates of DNMT3A-dependent oxidation of C to mC, of TET-dependent oxidation of mC to hmC, and of subsequent demethylation (hmC to C). We uncovered thousands of regions that undergo methylation conversion during developmental stages and reach equilibrium in the adult cortex. We observed significant differences in the overall rate of cytosine methylation state changes between the neuronal subtypes. Notably, we discovered a subset of genomic regions that, in contrast to the genome-wide pattern, lose both mC and hmC at CG sites during postnatal brain development. Functional annotation and motif analysis showed that these regions are predominantly enriched in enhancers and binding sites for immediate early genes, such as EGR1. Furthermore, we observed age-related strand-asymmetry in methylation patterns of both mC and hmC at CG sites in both neuronal subtypes. For the most highly expressed genes, hmC increases over the lifespan on both the sense and antisense strands. However, this increase is more pronounced on the sense strand, resulting in an age-dependent asymmetric pattern of hmC.
In summary, our study provides a comprehensive analysis of methylation and hydroxymethylation dynamics in two major neuronal subtypes. It highlights distinct patterns of epigenetic modifications across various genomic regions and through different postnatal developmental stages.

Disclosures: H. Xu: None. **J. Chien:** None. **J. Li:** None. **R. Vadukapuram:** None. **A. Kozlenkov:** None. **Y. Wei:** None. **C. Liu:** None. **S. Dracheva:** None. **E.A. Mukamel:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.17/Y22

Topic: I.02. Systems Biology and Bioinformatics

Title: Nonsense-mediated mRNA Decay Suppresses Neuronal Genes in the Developing Brain

Authors: *K. HU, R. YANG, X. FENG, Y. YANG, X. ZHANG;
Dept. of Human Genetics, The Neurosci. Inst., Univ. of Chicago, Chicago, IL

Abstract: Unproductive splicing, or alternative splicing coupled to nonsense-mediated mRNA decay (AS-NMD), plays a profound role in gene regulation and brain development. However, the identification of specific AS events that render transcripts to become NMD targeting remains limited. To address this gap, we developed the bioinformatics tool EANMD to identify the unproductive splicing events. EANMD exhibits high accuracy in annotating AS-NMD events in

Upf1 knockdown samples. Our further analysis revealed developmentally regulated NMD exons in the mouse brain, which plays a prominent role in suppressing synaptic genes. Notably, AS-NMD differentially regulates dozens of causal genes for neurodevelopmental disorders, suggesting their potential roles in disease pathogenesis.

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

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.18/Y23

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH RF1MH128695

Title: Developmental gene regulatory network atlas reveals dynamics of gene regulation in neurogenesis

Authors: *K. M. HANTHANAN ARACHCHILAGE[1], J. SHENG[2], R. RISGAARD[3], P. KUMARAGE[4], J. CHOI[2], A. M. SOUSA[5], D. WANG[6];
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Abstract: Understanding the complex dynamics of gene expression and regulation in the developing brain remains elusive, particularly at single-cell level. The continuously increasing developmental single-cell RNA-seq (scRNA-seq) datasets across brain regions and species allow us to further understand gene regulatory networks (GRNs) linking transcription factors to target genes, a cellular-level mechanism controlling developmental gene expression. However, the lack of comprehensive computational frameworks to capture the variations in GRNs along developmental stages has hindered our overall understanding of how different GRNs govern the developmental specification and maturation of different cell types. To address this, we propose a novel computational framework that integrates state-of-the-art techniques for pseudotime/lineage inference and network prediction to reveal various cell developmental trajectories (i.e., lineages) and underlying dynamics of GRNs along those lineages. The proposed computational framework not only identifies TF activity variations along a cellular lineage but also highlights cooperative TF interactions. To this end, the framework consists of five steps: 1) Pseudotime inference and identification of cells belonging to particular developmental process of interest (i.e., neurogenesis, cell differentiation), 2) Generate a GRN using the gene expression of the identified cells, 3) Examine the enrichment of regulons (TFs and their target genes) in each cell, 4) Identity dynamically varying regulons using a spatial autocorrelation technique, Moran's I test, by examining pseudo-temporally varying TF activity, 5) A deep learning model to predict target

gene expression and measure interaction effects between TFs. We demonstrated that our framework predicts lineage-specific GRNs for neurogenesis in the first trimester of human and macaque brain development, covering not only the distinct major forebrain regions (telencephalon, diencephalon) but also across excitatory and inhibitory neuronal lineages. We are expanding our analysis to additional subregions across different species (human, mouse, macaque) to investigate regional-, hierarchical-, and species-specific gene regulatory networks of neurogenesis (over 20 lineages). Moreover, our framework is open source, enabling researchers to investigate any developmental biological process. Additionally, we offer an interactive platform using Shiny for network visualization and exploration.

Disclosures: K.M. Hanthanan Arachchilage: None. **J. Sheng:** None. **R. Risgaard:** None. **P. Kumarage:** None. **J. Choi:** None. **A.M. Sousa:** None. **D. Wang:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.19/Y24

Topic: I.02. Systems Biology and Bioinformatics

Title: Characterizing the role of m6A and FTO in the amygdala during a model of social instability stress using a novel FTO fused Apobec1

Authors: *L. HATEGAN[1], B. J. WALTERS[2];
[1]Cell & Systems, Univ. of Toronto, Toronto, ON, Canada; [2]Biol., Univ. of Toronto Mississauga, Mississauga, ON, Canada

Abstract: Adolescence is a sensitive period of neurodevelopment. In mammals, psychological stress responses are regulated by the hypothalamus-pituitary-adrenal (HPA) axis, which is known to be hyperactive in adolescence. Recently, the N6-Methyladenosine (m6A) demethylase, fat, mass, and obesity-associated (FTO) protein has been implicated in the regulation of the HPA axis, whereby its absence leads to increased stress-response molecules such as corticosterone in blood plasma. To model stress *in-vivo*, rats were subjected to a social instability stress (SIS) paradigm. 32 rats, 16 females and 16 males were either isolated for 1 hour and cage swaped each day (stressed) or not (naïve) between P30-P45. 16 rats, 8 male, 8 female were sacrificed immediately following SIS (P45), or at the end of their adolescent developmental stage (P75). Their amygdala's were sub-dissected and RNA harvested. To understand the role of m6A and FTO in SIS in the amygdala, a mutagenic sequencing method exploiting the m6A consensus DRACH motif was developed. FTO was fused to the cytidine deaminase Apobec1, which converts cytosine to uracil. This construct was expressed using a cell free methodology and applied directly to total RNA, whereby it binds and demethylates m6A, while Apobec1 mutates the conserved cytosine to a uracil, allowing SNP calls to be made where m6A is localized. Additionally, utilizing DART-seq, which fused the m6A binding domain of YTH readers to Apobec1, global m6A profiling between stressed and naïve rat amygdala's was also conducted.

Between the two constructs, a large bias to the 3' UTR where m6A sites are hypothesized to be concentrated was determined, with the FTO fused Apobec1 showing more uniform distributions in the CDS suggesting a differential targeting methodology between the two constructs. Additionally, 158 transcripts were tagged by FTO fused Apobec1 that were not found in YTH fused Apobec1. This study shows, for the first time, where the precise localization of FTO is in relation to m6A and how m6A levels are altered under SIS, building on previous work of the role of FTO and m6A under stress.

Disclosures: L. Hategan: None. **B.J. Walters:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.20/Y25

Topic: I.02. Systems Biology and Bioinformatics

Title: Structural Neuromics as a Novel Neuropeptide Discovery Pipeline

Authors: *M. GLUCKSMAN[1], K. PHILIBERT[2], X. SHAO[3], C. YANG[4];
[1]Ctr. for Proteomics & Mol. Therapeut., Chicago Med. School/RFUMS, North Chicago, IL; [2]Ctr. for Proteomics and Mol. Therapeut., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL; [3]Ctr. for Proteomics & Mol. Therapeut., Rosalind Franklin Univ., North Chicago, IL; [4]Midwest Proteome Ctr., Rosalind Franklin Univ., North Chicago, IL

Abstract: The number of orphan receptors implies that many peptide ligands are yet to be discovered, characterized, and their regulation revealed. Our laboratory uses a proprietary neuromics discovery pipeline to unveil novel neuropeptide substrates by consolidating a workflow: biochemical, structural, and systems-based proteomic approaches, including *in silico* molecular modeling, mass spectrometry, enzyme kinetics, and X-Ray crystallography. As proof-of-concept, we examined the ability to reveal novel substrates of two closely related neuropeptide processing enzymes that published literature reports to cleave ~10 identical substrates; most recently, we added the reproductive regulator kisspeptin. EC 3.4.24.15 (EP24.15; thimet oligopeptidase) and EC 3.4.24.16 (EP24.16; neurolysin) are *classically* distinguished solely by the difference in a bond hydrolyzed in neurotensin; hence, the name Neurolysin. **XENIN 8/25:** in the gastrointestinal tract plays a role in regulating appetite, digestion, and glucose metabolism to influence gastric emptying and insulin secretion. Its C-terminal sequence is similar to neurotensin. **SPEXIN/NEUROPEPTIDE Q**: a 14-amino peptide binds to its cognate Galanin 2/3 receptor and through the gut-brain axis influences energy metabolism by inhibiting food intake, insulin resistance, and lipid absorption and reduces appetite, body mass, and stress responses. It is implicated in diabetes and nonalcoholic fatty liver disease. **NEURONOSTATIN-13:** encoded by somatostatin; regulates appetite, glucagon secretion and energy metabolism. A potential target for obesity and diabetes. **NEUROKININ A**: a member of the tachykinin family, functions in neuroendocrine regulation with kisspeptin and

dynorphin. And involved in inflammation and immune responses, cardiovascular function and smooth muscle contraction. **NOCICEPTIN/ORPHANIN FQ**: modulates pain perception via the NOP receptor, stress responses in the HPA axis via cortisol, mood regulation, and appetite/ feeding behavior. **NEUROPEPTIDE FF**: modifies pro- and anti-nociceptive pain perception, stress responses through cortisol, autonomic cardiovascular regulation, and reproduction via gonadotropin-releasing hormone (GnRH) to affect mating behavior and fertility. The results of this study add to the repertoire of these neuropeptide processing enzymes and represent an additional regulatory mechanism of mammalian neurophysiology mediated by peptide neurotransmitters. The data presented herein will provide insights into the development of novel therapeutic targets for the treatment of various neurological disorders and open new vistas for exploring brain functions.

Disclosures: M. Glucksman: None. **K. Philibert:** None. **X. Shao:** None. **C. Yang:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.21/Y26

Topic: I.02. Systems Biology and Bioinformatics

Title: Fast and Accurate Spatial Domain Detection for Spatial Transcriptomics: A Functional-PCA Approach

Authors: *A. P. BURNS[1], P. DONELLI[5], Z. MORRISSEY[2], A. PALUMMO[5], E. ARNONE[7], B. B. BENDLIN[8], O. LAZAROV[3], L. M. SANGALLI[6], L. HE[9], A. LEOW[4];
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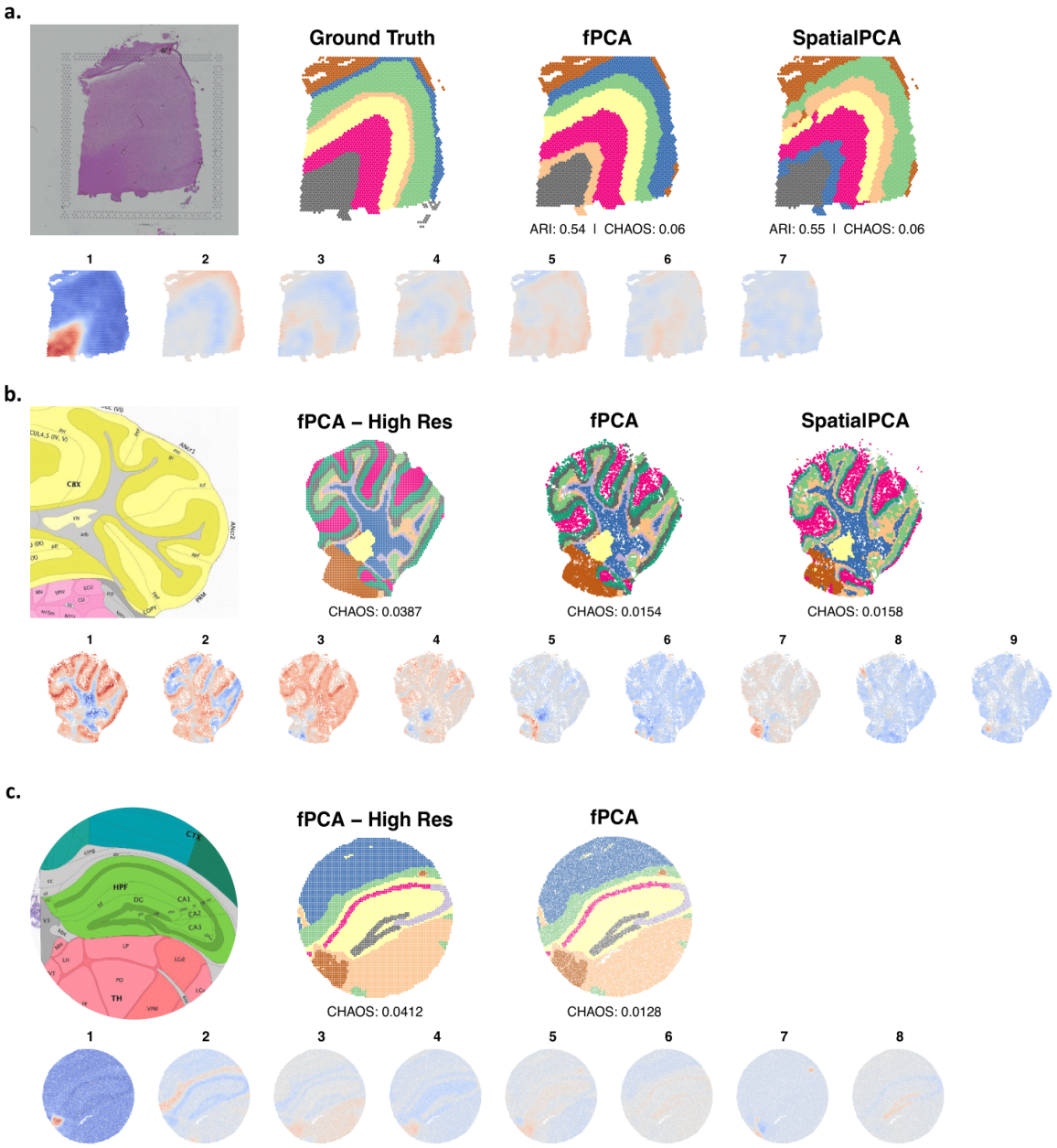
Abstract: **Background:**Spatial Transcriptomics measures gene expression while retaining expression location. Analyzing gene expression in spatial contexts is crucial for neuroscientists, as brain activity and its corresponding cellular and molecular signatures have unique region- or circuit-specific patterns that are otherwise lost without spatial information. However, existing computational methods to define spatial domains in biological tissue are slow and often restricted to predefined patterns, compromising both flexibility and accuracy. We introduce a dimension reduction algorithm that is faster and achieves comparable or better accuracy than leading methods.
Method: Our Functional-PCA algorithm combines Principal Component Analysis and Finite Element Analysis to analyze genetic expression data, leveraging spatial information. We tested its adaptability across four Spatial Transcriptomics technologies (ST, Visium, SlideSeq, Slideseq V2) and three neurological tissues (human Dorsolateral Prefrontal Cortex, mouse cerebellum, and mouse hippocampus), using pathologist annotations as ground truth for the human dataset.

Accuracy was assessed using the Adjusted Rand Index and CHAOS clustering metrics.
Results: Functional-PCA demonstrated significant speed improvements, usually between 10- to 1000-fold faster than a leading method depending on the dataset complexity, with consistent accuracy enhancements across different neurological tissues. Further validation on a test dataset confirmed its superior accuracy on both simple and complex domains. We show visualizations of Functional-PCA's spatial domain clustering to identify anatomical regions along with its accuracy for three neurological tissues [**FIGURE 1**].
Conclusion: The Functional-PCA approach significantly improves runtime by at least 10-fold while maintaining or enhancing accuracy for spatial domain detection in spatial transcriptomics. This method supports high-resolution domain reconstruction and has potential applications in 3D spatial domain detection and trajectory inference.



Disclosures: A.P. Burns: None. **P. Donelli:** None. **Z. Morrissey:** None. **A. Palummo:** None. **E. Arnone:** None. **B.B. Bendlin:** None. **O. Lazarov:** None. **L. He:** None. **A. Leow:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.22/Y27

Topic: I.02. Systems Biology and Bioinformatics

Support: CONACYT Grant 320520

Title: Molecular mimicry between Toxoplasma gondii B cell epitopes and neurodevelopmental proteins: An immunoinformatics approach

Authors: *T. BLANCO AYALA[1], K. MEZA-SOSA[2], D. VALLE-GARCIA[3], H. GONZÁLEZ[3], B. PINEDA OLVERA[4], G. PEREZ DE LA CRUZ[5], V. PEREZ DE LA CRUZ[6]; [2]Neurobioquimica y Conducta, [1]Inst. Nacional de Neurologia y Neurocirugia, Ciudad de Mexico, Mexico; [3]Inst. Nacional de Neurologia y Neurocirugia, Ciudad de México, Mexico; [4]NEUROINMUNOLOGIA, INSTITUTO NACIONAL DE NEUROLOGIA Y NEUROCIRUGIA, Ciudad de Mexico, Mexico; [5]Facultad de Ciencias, Mexico City, Mexico; [6]Lab. de Neurobioquímica y Conducta, Inst. Nacional de Neurologia Y Neurocirugia, Ciudad de Mexico, Mexico

Abstract: Epidemiological studies and metanalysis have shown an association between high seroprevalence of *T. gondii* and schizophrenia, particularly showing that schizophrenic patients have higher levels of anti-Toxoplasma immunoglobulins M and G (IgM and IgG) than controls. Previously, in a rat model, we showed that the progeny of mothers immunized prior to gestation with T. gondii lysates had behavioral and social impairments during adulthood. We suggested as a possible triggering mechanism, the existence of molecular mimicry between the parasite and host brain proteins. The aim of this study was to identify the occurrence of antigenic mimicry between *T. gondii* epitopes and host brain proteins. Through a bioinformatics analysis, we predicted *T. gondii* B cell epitopes and compared them with membrane proteins involved in the differentiation of neurons, astrocytes, oligodendrocytes, and microglia. We found a significant overlap between *T. gondii* immunogenic peptides and brain developmental proteins, as compared to other surface proteins not related to brain development, which supports our antigenic mimicry hypothesis. We found many proteins important for brain function and development such as BMP and Notch receptors as potential targets for *T. gondii*-induced antibodies. The epitopes identified in our analysis could be useful to better understand and possibly prevent the offspring behavioral and cognitive defects induced by pre-gestational *T. gondii* exposure.

Disclosures: T. Blanco Ayala: None. **K. Meza-Sosa:** None. **D. Valle-Garcia:** None. **H. González:** None. **B. Pineda olvera:** None. **G. Perez de la Cruz:** None. **V. Perez De La Cruz:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.23/Web Only

Topic: I.02. Systems Biology and Bioinformatics

Title: Peripheral Blood Gene Expression in Major Depressive Disorder: Identification of Candidate Biomarkers and Therapeutic Targets through Bioinformatics Analysis

Authors: *A. PATIL[1], K. TIWARI[2];
[1]All India Inst. of Med. Sci. Nagpur, Nagpur, India; [2]All India Inst. of Med. Sci., Nagpur, India

Abstract: Major depressive disorder (MDD) poses a significant burden on individuals and society. Diagnosis relies heavily on clinical interviews, constrained by the availability of specialized psychiatrists and subjectivity. Moreover, a substantial portion of patients doesn't respond to initial treatment, escalating the risk of treatment-resistant depression. Hence, the quest for biomarkers to aid diagnosis and assess drug response is pressing.This bioinformatic study aims to pinpoint potential biomarker genes in peripheral whole blood of MDD patients. Leveraging two distinct datasets from the Gene Expression Omnibus (GEO) database, GSE201332 (20 MDD patients) and GSE32280 (8 MDD patients) for discovery and validation phases respectively, we compared gene expression profiles against age-matched healthy controls using unpaired t-tests. Rigorously, Experimenter 1 processed the initial dataset, and Experimenter 2 analyzed the validation set in a blinded manner.In the discovery dataset, 18,954 genes were significantly upregulated, and 12,852 genes downregulated in MDD patients ($p < 0.05$). Of these, CTSB was upregulated in both datasets, while nine genes (CXCL3, NET1, DCAF8, METTL8, DLG1, B3GNT2, RACGAP1, FBXO22, WDR42A) were downregulated across both datasets. Protein-protein interaction analysis unveiled associations with noradrenaline transporter regulation, synaptic modification, protein degradation, cell proliferation, inflammation, and tumorogenesis.Notably, CTSB's upregulation aligns with its implication in depression and anxiety regulation. CXCL3, linked to neurofunction, showed downregulation, consistent with its role in modulating synaptic transmission and suicidal behavior. NET1's downregulation contradicts previous brain studies but could be relevant in other contexts. METTL8's involvement suggests a connection between gut microbiota and depression.These gene insights into depression's pathophysiology propose their potential as biomarkers or therapeutic targets warranting further exploration.

Disclosures: A. Patil: None. **K. Tiwari:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.24/Y28

Topic: I.02. Systems Biology and Bioinformatics

Support: NCI CCSG P30 CA060553
the Brain & Behavior Research Foundation (2018 Young Investigator Grant, 27793)
an Individual Biomedical Research Award from The Hartwell Foundation
NIH R01MH130428
CHDI foundation

Title: Neuron type-specific proteomics reveals distinct Shank3 proteoforms in iSPNs and dSPNs lead to striatal synaptopathy inShank3B$^{-/-}$mice

Authors: *Y.-Z. WANG[1], T. PEREZ-ROSELLO[2], S. SMUKOWSKI[3], D. SURMEIER[4], J. N. SAVAS[5];
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Abstract: Combinatorial expression of postsynaptic proteins underlies synapse diversity within and between neuron types. Thus, characterization of neuron-type-specific postsynaptic proteomes is key to obtaining a deeper understanding of discrete synaptic properties and how selective dysfunction manifests in synaptopathies. To overcome the limitations associated with bulk measures of synaptic protein abundance, we developed a biotin proximity protein tagging probe to characterize neuron-type-specific postsynaptic proteomes in vivo. We found Shank3 protein isoforms are differentially expressed by direct and indirect pathway spiny projection neurons (dSPNs and iSPNs). Investigation of Shank3B-/- mice lacking exons 13-16 within the Shank3 gene, reveal distinct Shank3 protein isoform expression in iSPNs and dSPNs. In Shank3B-/- striatum, Shank3E and Shank3NT are expressed by dSPNs but are undetectable in iSPNs. Proteomic analysis indicates significant and selective alterations in the postsynaptic proteome of Shank3B-/- iSPNs. Correspondingly, the deletion of exons 13-16 diminishes dendritic spine density, reduces spine head diameter, and hampers corticostriatal synaptic transmission in iSPNs. Remarkably, reintroducing Shank3E in adult Shank3B-/- iSPNs significantly rectifies the observed dendritic spine morphological and corticostriatal synaptic transmission deficits. We report unexpected cell-type specific synaptic protein isoform expression which could play a key causal role in specifying synapse diversity and selective synapse dysfunction in synaptopathies.

Disclosures: Y. Wang: None. **T. Perez-Rosello:** None. **S. Smukowski:** None. **D. Surmeier:** None. **J.N. Savas:** None.

Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.25/Y29

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Common Fund, NIH Office of the Director, Award OT2 OD030541 SPARC Program

Title: Accessing and Exploring the SPARC Connectivity Knowledge Base of the Autonomous Nervous System (SCKAN)

Authors: F. T. IMAM[1], T. H. GILLESPIE[1], I. ZIOGAS[2], M. C. SURLES-ZEIGLER[1], B. DE BONO[3], I. OZYURT[1], S. DALLOUL[4], D. DEL PIANO[4], V. LONGANI[4], S. MACE[4], A. PINTO[4], Z. SINNEMA[4], S. B. SÁ[4], D. KRISHNA[4], J. BOLINE[5], A. E. BANDROWSKI[1], S. J. TAPPAN[6], *J. S. GRETHE[1], M. E. MARTONE[1];
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Abstract: The NIH Common Fund's Stimulating Peripheral Activity to Relieve Conditions (SPARC) program aims to enhance our understanding of autonomic nervous system (ANS) connectivity to develop more effective bioelectronic medicine. A core component of SPARC, the SPARC Connectivity Knowledgebase of the ANS (SCKAN), integrates connectivity knowledge distilled from various authoritative sources through rigorous curation processes. SCKAN is a sophisticated knowledge base housing a rich collection of neuron populations with detailed phenotypic specifications and provenance. Connectivity is specified through the locations of cell bodies, axons, and axon terminals for these populations based on the Neuron Phenotype Ontology (NPO). SCKAN is a powerful resource to populate, reason, enhance, and query connectivity across multiple scales. However, because of its formal, ontological intricacies, accessing and comprehending SCKAN's wealth of information can be challenging, especially for the broader scientific community. The intrinsic complexity of neural connectivity also makes SCKAN challenging to explore. SCKAN's basic connectivity can be explored through SPARC's interactive connectivity maps (https://sparc.science/apps/maps); however, a map-based interface is not necessarily the most flexible or comprehensive way to explore SCKAN's content. In this poster, we present additional software tools we've developed to make accessing and exploring SCKAN more flexible for a broader scientific audience. These include: a) Simple SCKAN, a query-friendly extension of SCKAN that makes queries dramatically simpler to write; b) a web interface called SCKAN Explorer that allows rapid retrieval of knowledge from SCKAN, c) an enhanced version of SCKAN Explorer called SCKANNER offering more flexible query, visualization, and summarization options; and d) a prototype of a ChatGPT-powered natural language interface (NLI) called SCKAN NLI. Leveraging the power of the GPT-4 Large Language Model, SCKAN NLI provides a flexible way to specify how the connectivities should be summarized and reported, enhancing comprehension beyond traditional interfaces. For example, when prompted with queries like "What are the connections from dorsal root ganglion

to heart? List the terminal structures first and then summarize the connectivity pathways.", SCKAN NLI can generate a tailored response recognizing the query requirement. The combination of these tools can offer useful mechanisms to explore the extent of SCKAN's coverage of ANS connectivity, find its knowledge gaps, expand its content, and aid in broadening SCKAN's scope beyond the ANS.

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Poster

PSTR373: Genomics, Proteomics, and Bioinformatics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR373.26/Y30

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Common Fund, NIH Office of the Director, Award OT2 OD030541

Title: A community tool for integration of existing and emerging knowledge of neuronal connectivity into the knowledge base SCKAN

Authors: *S. TAPPAN[1], T. GILLESPIE[2], F. T. IMAM[3], I. ZIOGAS[4], I. OZYURT[5], D. DEL PIANO[6], Z. SINNEMA[6], A. PINTO[6], S. DALLOUL[6], V. LONGANI[6], D. KRISHNA[6], S. B. SÁ[6], S. FATTORI[6], M. C. SURLES-ZEIGLER[3], J. BOLINE[7], J. S. GRETHE[8], M. E. MARTONE[2];
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Abstract: The SPARC Portal (https://sparc.science) utilizes the computational reasoning power of SCKAN, a semantic knowledge base providing PNS connectivity data from literature and domain sources, to host a visual atlas (along with other in-development tools). We present major updates to the knowledge curation pipeline feeding SCKAN. Three distinct information sources (automated selection of topical literature, SPARC Portal user feedback, and expert in-depth topic expansion) are pulled into a single pipeline via the web-based authoring interface, Composer. SCKAN represents neuron populations using standardized application of the Neuron Phenotype Ontology (NPO), and draws from SPARC vocabularies (using InterLex), which supports preferred names and synonyms for anatomical and physiological phenotypes. Composer has a web-based interface that allows us to easily visualize and interact with these different pieces of infrastructure with the end result of reducing human error and effort. Composer supports the

extension of NPO to convey the complexity of diverse peripheral nerve trajectories through layers and across regions to multiple destinations by dynamically drawing for real-time verification. To streamline the extraction and upkeep of knowledge from literature sources, a Natural Language Processing pipeline runs monthly and employs a domain-specific, discriminatively pre-trained transformer deep learning model for relation extraction. Using an SVM classifier, it identifies sentences containing connectivity relationships defined by SPARC vocabulary. Isolated sentences are evaluated for relevance according to predetermined criteria, and formulated into connectivity-relevant statements in Composer. To expand SCKAN content, knowledge experts create knowledge statements about broad topics, such as the male and female reproductive systems. These system-level knowledge statements can be linked as “forward connections" into circuits. Changes to linked population statements are automatically monitored to ensure validity. Knowledge augmentation to correct or extend SCKAN can be submitted on the SPARC Portal with a map annotation tool which is passed to Composer for evaluation and incorporation into the referenced neuron populations. SPARC’s PNS connectivity mapping continues to serve as a robust use-case for Composer, and we look forward to the growth of its user-base with SPARC and in other research domains.

Disclosures: S. Tappan: None. **T. Gillespie:** None. **F.T. Imam:** None. **I. Ziogas:** None. **I. Ozyurt:** None. **D. Del Piano:** A. Employment/Salary (full or part-time):; MetaCell LLC. **Z. Sinnema:** A. Employment/Salary (full or part-time):; MetaCell LLC. **A. Pinto:** A. Employment/Salary (full or part-time):; MetaCell LLC. **S. Dalloul:** A. Employment/Salary (full or part-time):; MetaCell LLC. **V. Longani:** A. Employment/Salary (full or part-time):; MetaCell LLC. **D. Krishna:** A. Employment/Salary (full or part-time):; MetaCell LLC. **S.B. Sá:** A. Employment/Salary (full or part-time):; MetaCell LLC. **S. Fattori:** A. Employment/Salary (full or part-time):; MetaCell LLC. **M.C. Surles-Zeigler:** None. **J. Boline:** None. **J.S. Grethe:** None. **M.E. Martone:** None.

Poster

PSTR374: Human Connectomics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.01/Y31

Topic: I.03. Anatomical Methods

Support: NIH SPARC 75N98022C00018
NIH SPARC OT2 OD025340
Duke Office of Commercialization and Translation

Title: Computational tools for efficient and accurate modeling of autonomic nerve stimulation

Authors: D. MARSHALL[1], M. HUSSAIN[1], E. PEÑA[2], A. SHOFFSTALL[3], W. M. GRILL[1], ***N. PELOT**[1];
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Abstract: Computational modeling of neural stimulation therapies enables analysis of mechanisms of action; design of electrode geometries, electrode placements, and stimulation parameters to improve therapeutic responses and reduce side effects; translation of therapies from preclinical studies to clinical application; and systematic clinical programming of devices to account for inter-individual variability. However, many modeling tools are computationally demanding and lack important anatomical realism. We designed and implemented next-generation models incorporating three-dimensional (3D) fascicular nerve morphology based on microCT imaging, recording of neural signals, and efficient and standardized stimulation of multi-compartment fibers. Despite the complex 3D fascicular structure of the human cervical vagus nerve, activation thresholds modeled by extruding one nerve cross section matched unexpectedly well the thresholds from true-3D models. The match required that the cross section used for extrusion was selected appropriately and that the nerve was deformed to conform to the cuff. Our models of nerve recording generated compound action potential shapes, latencies, and magnitudes comparable to in vivo data for myelinated fibers, but not for unmyelinated fibers, and our novel approach reduced compute time by orders of magnitude compared to prior methods. We developed a Python package (PyFibers) to simulate the response of nerve fiber models to extracellular stimulation, based on the NEURON simulation environment. PyFibers includes many published fiber models, validated against their original implementations, and users can readily integrate additional models and stimulation protocols. We designed a surrogate nerve fiber model that enables simulation of activation thresholds orders of magnitude faster than the standard McIntyre-Richardson-Grill (MRG) model of a myelinated mammalian peripheral axon, while maintaining accuracy. The surrogate retains biophysical detail along the fiber, from transmembrane potential to gating parameters. Complex stimulation parameters that achieve selective activation of target fibers in human and pig vagus nerves were optimized within minutes on a single GPU, rather than hours on a large compute cluster or days to weeks on a local computer. Our advances in computational modeling of nerve stimulation will accelerate the design process in preclinical stages and will be invaluable in the clinical programming of nerve stimulation devices. Efficient approaches are essential to tractable modeling of multimodal imaging data being collected across numerous individuals and nerve locations.

Disclosures: D. Marshall: None. **M. Hussain:** None. **E. Peña:** None. **A. Shoffstall:** None. **W.M. Grill:** None. **N. Pelot:** None.

Poster

PSTR374: Human Connectomics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.02/Y32

Topic: I.03. Anatomical Methods

Support: NIH SPARC 75N98022C00018

Title: Title: Anatomically-Aware Deep Learning for Accurate 3D Segmentation of Fascicles in the Human Vagus Nerve

Authors: *J. ZHANG[1], P. BALABHADRA[1], O. MISTRY[1], A. UPADHYE[2], J. CHIN[1], A. SHUNMUGAVEL[1], D. WILSON[1], M. W. JENKINS[1], N. A. PELOT[3], A. SHOFFSTALL[1]; [1]Case Western Reserve Univ., Cleveland, OH; [2]Biomed. Engin., Case Western Reserve Univ., Cleveland Heights, OH; [3]Biomed. Engin., Duke Univ., Durham, NC

Abstract: Objective. Vagus nerve stimulation (VNS) targets the primary pathway of the parasympathetic autonomic nervous system to treat conditions such as epilepsy, depression, inflammatory disorders, cardiovascular diseases, and metabolic issues. However, its efficacy is often compromised by side effects due to off-target stimulation. It is thus crucial to better understand the neural pathways within the human vagus nerve (VN) through quantitative analysis and computational modeling of the nerve's responses to VNS. Micro-computed tomography (microCT) imaging resolves the complex 3D fascicular structure of the VN, but current 2D segmentation methods only process individual image slices and do not leverage the 3D context provided by microCT, often missing connectivity and boundary details of the VN fascicles. These errors can lead to inaccuracies in anatomical quantifications and computational modeling of VNS. Here, we introduce a robust, deep learning-based automated 3D segmentation workflow that delineates both fascicle and the outer nerve (epineurium) boundaries with accurate anatomy. Method. We used a 3D U-Net convolutional neural network (CNN) architecture, enhanced with residual connections to maintain contextual information in the images. During network training, we introduced a novel loss function designed to prevent topological errors, such as fascicle pixels coming into direct contact with the background. We used the 2D U-Net for baseline comparison and validated each approach's performance through four-fold cross-validation. For model evaluation, we used traditional metrics like Dice scores and added measures that assess anatomical plausibility, including quantified inter-slice jittering, centerline-aware Dice score (cl-Dice), and fascicle false detection rates. Results. The 3D workflow outperformed the 2D network in segmentation accuracy when compared to manual segmentation. It achieved an average Dice score of 0.94 versus 0.87 for the 2D model, and reduced inter-slice jittering for fascicles and epineurium by 4x and 2.7x, respectively. The cl-Dice score increased from 0.89 to 0.93, indicating better preserved topology. Also, the average fascicle false positive rate decreased by 21%. Conclusion. We developed an automated pipeline to segment the complex three-dimensional fascicular structure of the human VN from microCT images, with more accurate results that will facilitate more precise analyses of nerve morphology and functional organization, as well as computational modeling with improved anatomical realism to inform the development of next-generation VNS techniques.

Disclosures: J. Zhang: None. **P. Balabhadra:** None. **O. Mistry:** None. **A. Upadhye:** None. **J. Chin:** None. **A. Shunmugavel:** None. **D. Wilson:** None. **M.W. Jenkins:** None. **N.A. Pelot:** None. **A. Shoffstall:** None.

Poster

PSTR374: Human Connectomics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.03/Z1

Topic: I.03. Anatomical Methods

Support: NIH SPARC 75N98022C00018

Title: The human vagal complex from brainstem to abdomen, from gross anatomy to microscopy in 25 cadavers

Authors: *A. SHOFFSTALL[1], N. A. PELOT[2], N. B. NUZOV[1], J. ZHANG[1], E. CINTRON[1], J. COLEMAN[1], A. UPADHYE[1], L. LUNASCO[1], B. BRUNSMAN[1], K. WORKMAN[1], C. KOLLURU[1], J. SECKLER[1], N. JOSEPH[1], J. CHIN[1], Y. KIM[1], M. SETTELL[3], K. TURK[2], A. SANTOS[2], K. LUDWIG[3], D. HERZKA[1], G. SALI[1], C. FLASK[1], A. BLITZ[1], A. SHUNMUGAVEL[1], D. WILSON[1], M. W. JENKINS[1], W. M. GRILL[2], A. CROFTON[1]; [1]Case Western Reserve Univ., Cleveland, OH; [2]Duke Univ., Durham, NC; [3]Univ. of Wisconsin-Madison, Madison, WI

Abstract: Background: The vagus nerve (VN) connects the brainstem to the cervical, thoracic, and abdominal organs. Mapping the gross morphology, anatomy, ultrastructure, and fiber types of the VN has tremendous potential to improve the efficacy and specificity of existing autonomic neuromodulation therapies and inform the designs of new therapies to target or avoid specific vagal fibers. We are conducting the most comprehensive mapping of the VN to date, from the perspectives of sample size, range of imaging modalities, nerve length, and imaging resolution. **Methods:** Embalmed cadavers (N=25) were imaged with a 3T MR scanner and then dissected from the brainstem to the abdomen with a novel approach enabling access to the complete vagal complex without moving the body. Using an optical stylus, we digitized the 3D coordinates of the vagal trunk, the proximal ~2 cm of each branch, and standardized anatomical landmarks. Nerve branches were painted for unique identification, and the vagal complex was removed in one piece. We stained the nerve with phosphotungstic acid (PTA), followed by low-resolution CT imaging (300 µm isotropic voxels) and microCT imaging (11.4 µm isotropic voxels). Portions of the nerve were then prepared for microscopy, with paraffin embedding for histology and immunohistochemistry, and resin embedding for 3D-MUSE (microscopy with ultraviolet surface excitation) block-face imaging. **Results:** The entire vagal complex, including the cervical, thoracic, and abdominal branches, was successfully removed en bloc; branches were labeled by the name of the target organ. Branch counts and patterns varied substantially across individuals. PTA staining enhanced microCT contrast of the fascicles against the surrounding epineurium, enabling automated segmentation of the complex 3D fascicular morphology. Initial analyses suggest that the fascicles of the recurrent laryngeal nerve (the primary branch responsible for off-target effects during vagus nerve stimulation therapy) merge with fascicles of the main trunk within a few millimeters from the branch point. Imaging data from MRI, 3D-tracing, microCT, histology, and 3D MUSE provide essential inputs to computational models of autonomic nerve stimulation to design and improve neuromodulation therapies. **Conclusions:** We have quantified the morphology, branching pattern, microstructure, and fascicular organization of the human VN to advance the VN anatomical knowledge base, and to identify novel neuromodulation targets, for neural stimulation therapies with high specificity through computational modeling. Our ongoing project will ultimately yield high-resolution imaging from N=50 cadavers.

Disclosures: A. Shoffstall: None. **N.A. Pelot:** None. **N.B. Nuzov:** None. **J. Zhang:** None. **E. Cintron:** None. **J. Coleman:** None. **A. Upadhye:** None. **L. Lunasco:** None. **B. Brunsman:**

None. **K. Workman:** None. **C. Kolluru:** None. **J. Seckler:** None. **N. Joseph:** None. **J. Chin:** None. **Y. Kim:** None. **M. Settell:** None. **K. Turk:** None. **A. Santos:** None. **K. Ludwig:** None. **D. Herzka:** None. **G. Sali:** None. **C. Flask:** None. **A. Blitz:** None. **A. Shunmugavel:** None. **D. Wilson:** None. **M.W. Jenkins:** None. **W.M. Grill:** None. **A. Crofton:** None.

Poster

PSTR374: Human Connectomics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.04/Z2

Topic: I.03. Anatomical Methods

Support: NIH's Stimulating Peripheral Activity to Relieve Conditions programs 75N98022C00018 and OT2 OD025340
US Dept. of Veterans Affairs 1IS1BX004384, the Cleveland VA APT Center
Case Western Reserve University

Title: Stains for microCT-based visualization of complex fascicular structures in the human vagus nerve

Authors: *M. REYNOLD[1], C. TSIPTSIS[2], J. ZHANG[2], N. B. NUZOV[3], N. A. PELOT[6], A. CROFTON[4], E. CINTRON[5], A. SHOFFSTALL[2];
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Abstract: Background: Micro-computed tomography (microCT) enables 3D visualization of fascicular structures in peripheral nerves stained with contrast agents. However, robust contrast of fascicular boundaries relative to the surrounding epineurium depends on the tissue stain. High quality and consistent perineurium contrast enables precise automated segmentation of fascicles; segmented images can be analyzed to quantify anatomy and used as inputs to anatomically realistic computational models of vagus nerve stimulation. Prior microCT imaging of peripheral nerves used iodine or osmium tetroxide (OsO4); herein, we compare staining using phosphotungstic acid (PTA) to past staining methods using human embalmed cadaveric vagus nerves. Methods: We sampled 6 cm of the cervical vagus nerve from 3 unidentified embalmed human cadavers, and divided each into three 2 cm sections. We stained each section with 1% Lugol's iodine, 2% osmium tetroxide, or 3% PTA. We imaged the samples using Scanco microCT 100 (3.3 μm isotropic voxel size). We quantified the perineurial contrast across the three stains by calculating the ratio of voxel intensities between the fascicle, perineurium, and interfascicular epineurium. Results: OsO4 and iodine-stained nerve images yielded poor contrast, unreliable staining, and other artifacts, with a low perineurium-to-fascicle contrast ratio. PTA-stained samples yielded consistent staining with a much better perineurium-to-fascicle contrast ratio. Further, we demonstrated the compatibility of PTA-stained nerve samples with

downstream histology, including H&E staining, trichrome staining, and immunohistochemistry. Conclusion: PTA provides clear fascicular contrast for visualizing complex human vagal morphology. PTA-stained tissues are compatible with subsequent histological staining and immuno-labeling which can provide unique advantages in terms of ease of segmentation and co-registration of modalities to build realistic models.

Disclosures: M. Reynold: None. **C. Tsiptsis:** None. **J. Zhang:** None. **N.B. Nuzov:** None. **N.A. Pelot:** None. **A. Crofton:** None. **E. Cintron:** None. **A. Shoffstall:** None.

Poster

PSTR374: Human Connectomics

Location: MCP Hall A

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Program #/Poster #: PSTR374.05/Z3

Topic: I.03. Anatomical Methods

Support: NIH SPARC 75N98022C00018

Title: Analysis of the human cervical vagus nerve and its connections to nearby neurovasculature

Authors: *L. LUNASCO[1], B. BRUNSMAN[1], Z. SAMBA[1], N. B. NUZOV[2], T. PASCOL[1], S. O'NEILL[1], S. SCHERER[1], M. BRIGGER[1], S. RUBIN[1], K. WORKMAN[1], S. BOKHARI[1], N. A. PELOT[3], A. SHOFFSTALL[2], A. CROFTON[1];
[1]Anat., [2]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH; [3]Biomed. Engin., Duke Univ., Durham, NC

Abstract: Vagus nerve stimulation (VNS) is FDA-approved for epilepsy, depression, obesity, and stroke with other indications in development. However, its use has been hindered by off-target side effects and limited efficacy. Understanding vagus nerve (VN) anatomy, particularly its interconnections with nearby neurovasculature, in the cervical region near the implant site, is crucial for improving VNS. To enhance this understanding, we developed a dissection technique that allows access to the complete vagus nerve (VN).We dissected the right and left cervical vagus nerves (cVN) in n=20 embalmed cadavers (10 F, 10 M), including its branches and other nearby nerves. We recorded the number and locations of VN branches to cervical targets and to other nerves. Small branches were confirmed via histologic imaging. The position of the cVN varied relative to the internal jugular vein and carotid arteries across cadavers and between sides within a single cadaver. The position of a single cVN in the carotid sheath even varied at different levels as it descended in the neck. We found a mean of 3 ± 3 branches on the right and 4 ± 4 branches on the left that traveled to the carotid arteries. The cVN shared epineurium with the hypoglossal nerve (CN XII) near the skull base in 100% of nerves, and once their epineurial sheaths were separate, there were up to 3 communicating branches between the cVN and CN XII on the right (60% had 0 communicating branches) and 4 on the left (55% had 0 communicating branches). The cVN had 0-2 communicating branches with the glossopharyngeal nerve (CN IX)

on the right (70% had 0 branches) and had 0-3 with the CN IX on the left (60% had 0 branches). Communicating branches with the accessory nerve were only observed in 2 cadavers (10%), both exhibiting bilateral connections. The cVN connected to the upper cervical spinal nerves (C1-5) in 45% of cadavers on the right, but only 35% on the left. The superior laryngeal nerve (SLN) showed remarkable consistency across cadavers with all specimens possessing right and left SLNs arising from the upper cervical region with similar inferomedial trajectories to the larynx. The pharyngeal branch was present in 70% of both right and left cVNs. There was a mean of 6 ± 5 branches connecting the right VN with the sympathetic trunk (ST) (range: 1-22) and 4 ± 3.6 branches between the left VN and ST (range: 0-15). Our results indicate immense gross anatomic variations of the cVN beyond prior reports in the literature. Understanding cVN's interactions with nearby neurovasculature is needed to optimize VNS electrode design and surgical implantation.

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Poster

PSTR374: Human Connectomics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.06/Z4

Topic: I.03. Anatomical Methods

Support: NIH SPARC 75N98022C00018

Title: Variations in thoracic human vagus nerve branches

Authors: *B. BRUNSMAN[1], L. LUNASCO[1], Z. SAMBA[1], N. B. NUZOV[2], T. PASCOL[1], S. SCHERER[1], M. BRIGGER[1], K. WORKMAN[1], S. BOKHARI[1], J. ZHANG[2], S. O'NEILL[1], N. A. PELOT[3], A. SHOFFSTALL[2], A. CROFTON[1,4];
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Abstract: Originating in the medulla and traveling through the cervical, thoracic and abdominal regions, the vagus nerve (VN) supplies many structures, including vital organs like the heart and lungs. Vagus nerve stimulation (VNS) provides a non-pharmacological treatment for a variety of disorders and has shown promise for treating heart failure, cardiac arrhythmias and improving recovery after myocardial ischemia. However, vagal innervation of the heart is complex and must be better understood for cardiac applications of VNS to advance. To improve understanding of cardiac innervation by the vagus nerves, we characterized the branches of the thoracic vagus nerves (tVN) from the clavicle to the start of the esophageal plexus in human cadavers. Cervical

VNs (cVN) and tVNs were dissected bilaterally in 20 embalmed cadavers (10 F, 10 M). The thoracic VN (tVN) was defined as the region from the clavicle to the superior end of the esophageal plexus. Branches were followed to their proximal targets to enable identification and their relationships relative to key anatomical landmarks were noted. There was a mean of 16 ± 6 (mean ± standard deviation) branches of the right tVN (range: 6-32) and 14 ± 5 branches of the left tVN (range: 3-22). The heart was supplied by 8 ± 5 vagal branches on the right (range: 2-25) and 10 ± 5 on the left (range: 2-19) with an additional 0-9 branches arising from the vagus and traveling to carotid vasculature. Since the carotid branches were not able to be traced distally, it is unclear if these branches were, in fact, cardiac branches. There was a mean of 1 ± 1 right cervical cardiac branches (45% had 0 branches; range = 0-4) and 1 ± 1 left cervical cardiac branches (40% had 0 branches; range = 0-5). There was a mean of 7 ± 4 right thoracic cardiac branches (mode = 6 in 30% of cases; range = 2-21) and 9 ± 4 left thoracic cardiac branches (mode = 4 in 15% of cases; range = 2-18). Additional cardiac branches arose from the esophageal plexus, but were not quantified due to large numbers. The respiratory tree was supplied by a mean of 11 ± 6 branches of the right tVN (range: 4-28) and by 6 ± 4 branches of the left tVN (range: 0-15). Branches supplying both the heart and lungs, termed cardiopulmonary branches, were present in 95% of cases (range: 0-17 branches; mean = 5 ± 4) on the right and in 70% of cases (range: 0-15 branches; mean = 3 ± 4) on the left. The relevance of and factors that affect the quantity of vagal branches supplying a target remains unknown but varies greatly, especially for the heart and lungs. However, a better understanding of tVN branching will help advance cardiac applications of VNS.

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Poster

PSTR374: Human Connectomics

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.07/Z5

Topic: I.03. Anatomical Methods

Support: NIH 75N98022C00018
DoD NDSEG Fellowship Program

Title: Statistical variation of the branching pattern of the human cervical vagus nerve using 3D tracing

Authors: *N. B. NUZOV[1], L. LUNASCO[2], B. BRUNSMAN[2], K. WORKMAN[2], N. OGRINC[2], Z. SAMBA[2], S. BOKHARI[2], N. A. PELOT[3], A. R. CROFTON[2,4], A. J. SHOFFSTALL[1]; [1]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH; [2]Anat., Case Western Reserve

Univ., Cleveland, OH; [3]Biomed. Engin., Duke Univ., Durham, NC; [4]Pathology and Cell Biology, University of South Florida, Tampa, FL

Abstract: The human vagus nerve (cranial nerve X) is the longest in the autonomic nervous system and carries the majority of parasympathetic fibers. Although vagus nerve stimulation (VNS) is used to treat epilepsy, depression, obesity, and stroke sequelae, many patients do not show substantial improvement and suffer from side effects. VNS is under investigation to treat many other conditions but the mechanism of action is not understood. Our novel method of 3D tracing enables digitization of the vagus nerve and its branches within a gross anatomic context; no other existing imaging modalities can visualize the trajectory of the entire human vagal complex.

We dissected human cadavers (n=6; 3F/3M) to expose the vagal trunk and branches with the body supine. We used an optically tracked stylus to trace the pathway of the vagus nerve in three dimensions from brainstem to abdomen, and collected points at anatomical landmarks. We followed each branch to its target organ to label it accordingly and traced the initial trajectory as distally as possible including its branching angle. We created representative 3D male and female body models from NIH Visible Human data, including the skeleton and major organs, which we scaled based on distances between the anatomical landmarks to enable co-registration to the vagal tracing data.

The co-registered 3D tracing and body model provides visualization of the pathway of the vagus nerve and its branches in an individual overlaid on representative anatomy to scale. Specific levels were marked on the vagus nerve in the same axial planes as the anatomical landmarks, which allows for standard comparison of branch locations between subjects while accounting for differences due to height. The number of branches to each target organ, locations of branches, and distances between branches varied substantially between the left and right sides, and across individuals. For example, we examined communicating branches between the vagus and the sympathetic trunk in the cervical region. A black female cadaver (87 y.o.) had 6 left and 5 right branches; 3 of which were between the vagus and the superior cervical ganglia (SCG). Conversely, a black male cadaver (77 y.o.) had 1 left and 9 right branches, with none connected to the SCG.

The current results are being extended across 50 cadavers of varying sex, age, and race to reveal trends. Locations of minimal or conserved branching across multiple subjects will expose potential VNS implant locations that may reduce off-target side effects and iatrogenic injury of branches during implantation. The co-registered data with the 3D body model will allow clinicians to plan surgical techniques to access novel neuromodulatory sites.

Disclosures: N.B. Nuzov: None. **L. Lunasco:** None. **B. Brunsman:** None. **K. Workman:** None. **N. Ogrinc:** None. **Z. Samba:** None. **S. Bokhari:** None. **N.A. Pelot:** None. **A.R. Crofton:** None. **A.J. Shoffstall:** None.

Poster

PSTR374: Human Connectomics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.08/Z6

Topic: I.03. Anatomical Methods

Support: NIH SPARC 75N98022C00018

Title: 3d microscopy with ultraviolet surface excitation of the human vagus nerve

Authors: J. SECKLER[1], *N. JOSEPH[1], I. MARSHALL[1], C. KOLLURU[1], K. YU[1], J. CHEN[1], R. ZHU[1], N. PETRANKA[1], N. A. PELOT[2], A. SHOFFSTALL[1], D. L. WILSON[1], M. W. JENKINS[1];
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Abstract: To inform the design of neuromodulation therapies, we are microscopically imaging and analyzing anatomy of the human vagus nerve (VN) in an effort to create a VN connectome. Three-dimensional microscopy with ultraviolet surface excitation (3D-MUSE) is a serial block-face technique which facilitates the visualization, measurement, and modeling of human vagus anatomy. This includes the complex 3D structure of the fascicles and perineurium, as well as the 3D pathways of fiber bundles within a fascicle and across fascicle splits and merges. 3D-MUSE bridges between macroscopic imaging techniques such as microCT and microscopic imaging techniques such as histology. Compared to microCT, 3D-MUSE is able to resolve smaller fascicles and enables segmentation of the perineurium in 3D. 3D-MUSE also provides 3D microscopic insights whereas histology operates on 2D cross sections. The 3D-MUSE workflow involves grossing embalmed human vagus nerves into 15 mm sections using a laser cutter, whole-mount staining with hematoxylin and rhodamine B, embedding tissue in glycol methacrylate, and imaging with our 3D-MUSE system. This imaging system consists of a microtome attached to a MUSE microscope which illuminates the sample with 280 nm light. This system automatically adjusts focus to the block face and sections to a thickness of 3 μm using a tungsten carbide knife. Our optical system uses an objective with 4x (0.13 numerical aperture) magnification. This system generates a 3D stack of ~5000 2D images from a 15 mm nerve sample. We developed self-supervised and supervised deep learning techniques trained on 5% of the cross sections of each sample to automatically segment the epineurium, perineurium, and fascicles with a Dice coefficient of greater than 0.92. A structure tensor analysis determines fiber orientation and estimates the 3D pathways of fiber clusters through the sample. We are quantifying the vagal anatomy from the automatic segmentations and fiber bundle tractograms, including fascicle size, perineurium thickness, fascicle splits/merges, fiber streamlines tortuosity, and changes in fiber bundle organization. These segmented morphology and tractograms serve as inputs to anatomically-realistic computational models of human vagus nerve stimulation; the high resistance of the perineurium increases stimulation thresholds while the tortuous fiber pathways decrease stimulation thresholds. This analysis provides a map of the nerve fiber bundle movement within and between fascicles along the length of the vagus nerve.

Disclosures: J. Seckler: None. **N. Joseph:** None. **I. Marshall:** None. **C. Kolluru:** None. **K. Yu:** None. **J. Chen:** None. **R. Zhu:** None. **N. Petranka:** None. **N.A. Pelot:** None. **A. Shoffstall:** None. **D.L. Wilson:** None. **M.W. Jenkins:** None.

Poster

PSTR374: Human Connectomics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.09/Z7

Topic: I.03. Anatomical Methods

Title: A novel classification schema for describing the human carotid sinus nerve

Authors: *S. O'NEILL[1], C. TSIPTSIS[2], S. SCHERER[1], B. BRUNSMAN[1], L. LUNASCO[1,3], N. A. PELOT[4], A. SHOFFSTALL[2], K. LUDWIG[5,6,7], A. CROFTON[1,8];
[1]Anat., Case Western Reserve Univ. Sch. of Med., Cleveland, OH; [2]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH; [3]Biomedical Engineering, Case Western Reserve University, Cleveland, OH; [4]Biomed. Engin., Duke Univ., Durham, NC; [5]Bioengineering and Neurolog. Surgery, Univ. of Wisconsin Madison, Madison, WI; [6]Wisconsin Institute for Translational Neuroengineering, Madison, WI; [7]Surgery, University of Wisconsin-Madison, Madison, WI; [8]Pathology and Cell Biology, University of South Florida, Tampa, FL

Abstract: The carotid sinus nerve (CSN) is a branch of the ninth cranial nerve (CN IX) that acts as the afferent limb of the carotid baroreflex. CSN electrostimulation presents a therapy for heart failure and hypertension. To characterize the anatomic diversity of the CSN and facilitate advancement in CSN neuromodulation, we developed a novel schema to describe CSN variants. From 20 cadavers (10 male, 10 female), a total of 34 CSNs (16 left, 18 right) were dissected from their origin off CN IX to their termination at the carotid sinus. Branching patterns of each CSN and aspects of nerve position including distance from major landmarks were recorded. The CSN most commonly descended along the anterolateral surface of the internal carotid artery (52.9%). Per our classification schema (Figure 1A), type III CSNs were the most common (44%), followed by type I (26.5%), type IV (20.6%), and type II (9%). The mean distance of the CSN origin off CN IX from key landmarks were: 15.9 ± 9.6 mm inferior to the jugular foramen, 14.9 ± 6.6 mm anterior to the styloid process, and 49.0 ± 7.5 mm medial to the anterior margin of the tragus. Frequency of CSN communication with other neural pathways is presented in Figure 1B. Our results provide insight into the anatomic variation that the CSN exhibits. Such findings will drive development of improved CSN electrodes and more accurately guide the surgical placement of such devices.

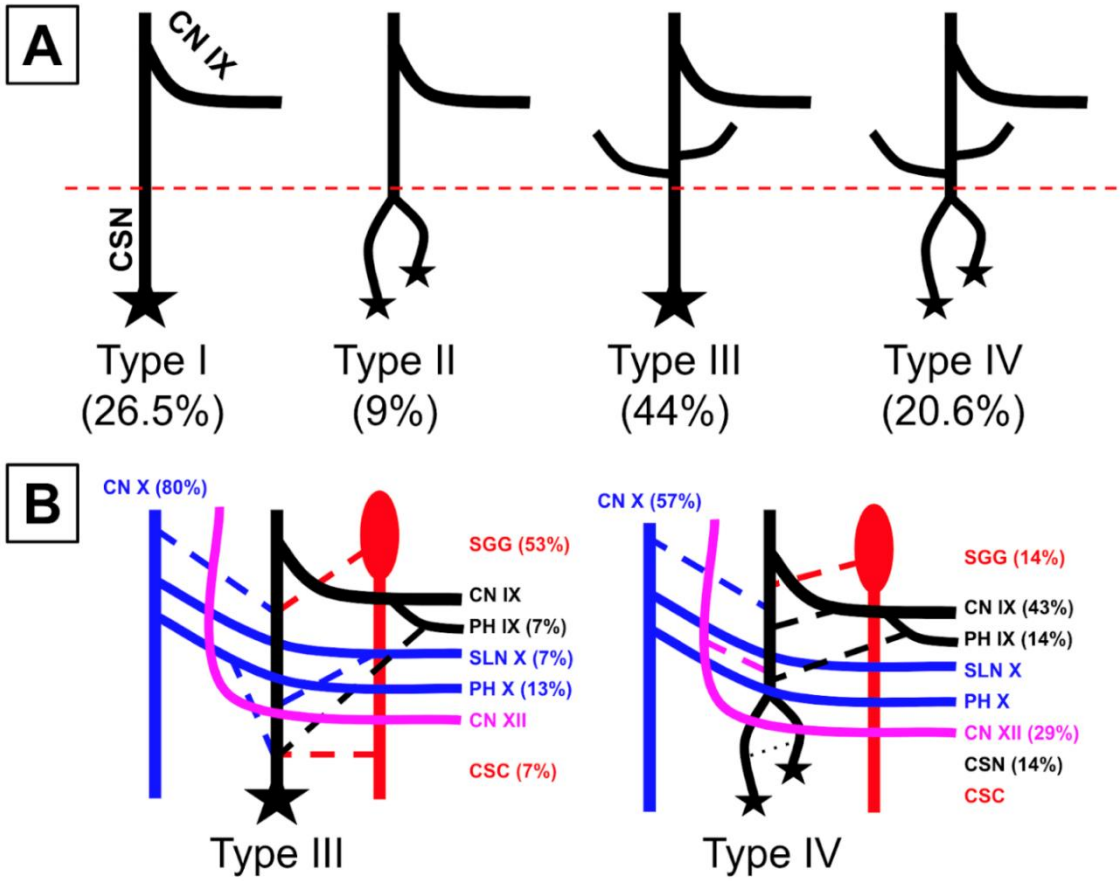

Figure 1. (**A**) Classification of CSN gross anatomy. Type I: single trunk from CN IX to carotid sinus. Type II: single trunk with ≥2 terminal branches. Type III: trunk with ≥1 connections to local nerves. Type IV: trunk with ≥1 connections to local nerves and ≥2 terminal branches. Red line: nerve transition point proximal to which terminal arborization does not occur. (**B**) Frequencies of communications between the CSN and other nerve pathways for type III (left) and type IV (right) CSN branching structures. CSC = cervical sympathetic chain; CN X = vagus nerve; CN XII = hypoglossal nerve; PH IX = pharyngeal branch of CN IX; PH X = pharyngeal branch of CN X; SLN X = superior laryngeal branch of CN X; SCG = superior cervical ganglion.

Disclosures: S. O'Neill: None. **C. Tsiptsis:** None. **S. Scherer:** None. **B. Brunsman:** None. **L. Lunasco:** None. **N.A. Pelot:** None. **A. Shoffstall:** None. **K. Ludwig:** None. **A. Crofton:** None.

Poster

PSTR374: Human Connectomics

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.10/Z8

Topic: I.03. Anatomical Methods

Support: NIH Grant 1R01EB033403-01
Multiscale Imaging of The Carotid Sinus Nerve (CVRx)

Title: Identifying potential sources of off-target activation from baroreflex activation therapy using microCT

Authors: *C. TSIPTSIS[1], S. O'NEILL[2], J. CHIN[2], S. WILKS[3], N. A. PELOT[4], K. LUDWIG[5], A. CROFTON[2], A. SHOFFSTALL[2];
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Abstract: Baroreflex activation therapy (BAT) involves an implanted device that electrically stimulates baroafferent fibers located in the carotid sinus nerve (CSN) to reduce blood pressure in patients with hypertension and improve symptoms in patients with heart failure. However, activation of off-target nerve fibers can cause paresthesia, dysphonia, and muscle twitches. In order to identify potential sources of off-target activation, we dissected six carotid arteries from embalmed human cadavers (6 Female) at the carotid bifurcation; the region was removed en bloc to preserve the gross structure of the tissue. We stained each sample with phosphotungstic acid and conducted microCT imaging using a Scanco μCT 100 (11.4 μm isotropic voxels). We identified and annotated key structures in each image, including vasculature (internal, external and common carotid arteries, and internal jugular vein), cranial nerves (CN IX, X, XII), branches of cranial nerves (CSN, superior laryngeal nerve), and other tissues (carotid body, sympathetic trunk (ST), ansa cervicalis (AS)). We measured approximate distances between the nerves relative to the reported BAT stimulation sites on the surface of the carotid sinus (CS). The distances between electrode sites and CN X were <1 cm. The ST and AS were within <1.2 cm of possible electrode locations. Cranial nerve X and its branches innervate several muscles involved in speech such as the cricothyroid muscle, which may produce voice hoarseness if activated. Similarly, AS innervates the omohyoid, sternohyoid and sternothyroid muscles, which could contribute to muscle twitching if activated. The region surrounding the CS contains dozens of fascicles from the cranial nerves and their branches, each acting as a potential source of activation. The degree of complexity and connectivity in the nerve plexus underscores the challenge of selective nerve activation in this region.

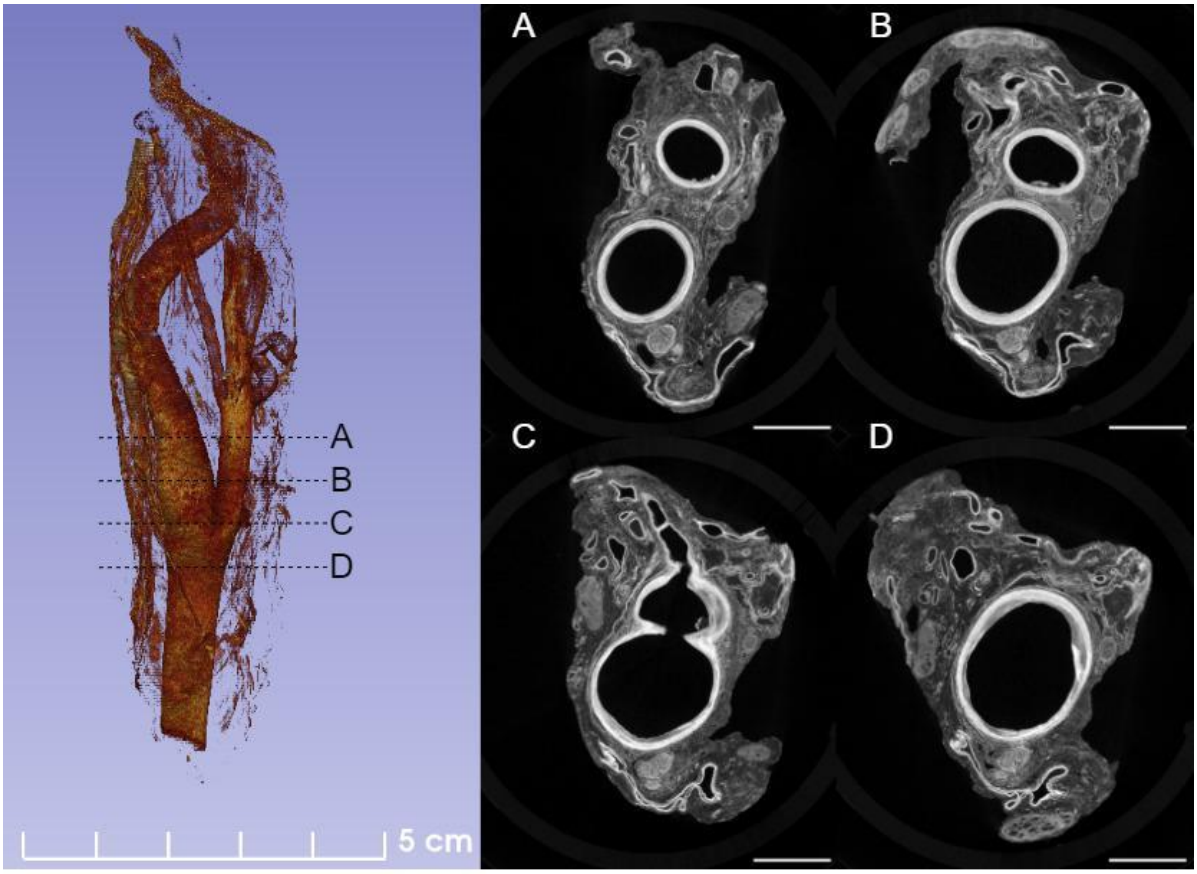

Figure 1. Left: Volume rendering of the carotid arteries with nearby nerves. Right: Transverse images of the tissue corresponding with the dashed lines on the left. The scale bar is 5 mm.

Disclosures: C. Tsiptsis: None. **S. O'Neill:** None. **J. Chin:** None. **S. Wilks:** A. Employment/Salary (full or part-time):; CVRx. **N.A. Pelot:** None. **K. Ludwig:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuronoff, NeuroOne Medical. F. Consulting Fees (e.g., advisory boards); Abbott, Cala Health, Blackfynn, Battelle, Neuronoff, Presidio Medical, Alfred Mann Foundation, ONWARD, Restora Medical, CVRx. **A. Crofton:** None. **A. Shoffstall:** A. Employment/Salary (full or part-time):; Neuronoff. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuronoff. F. Consulting Fees (e.g., advisory boards); Neuronoff.

Poster

PSTR374: Human Connectomics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.11/Z9

Topic: I.03. Anatomical Methods

Support: 1R21-HD-101964-01A1
7R21-HD101964-02
P20-GM-103446
5P20-GM-103653

Title: Translating Time maps the timeline of brain white matter pathway maturation from mice to humans

Authors: M. BRYANT[1], K. OFORI[2], N. COTTAM[2], J. ROGGE[1], J. SUN[2], ***C. CHARVET**[1]; [1]Col. of Vet. Med., Auburn Univ., Auburn, AL; [2]Biol. Sci., Delaware State Univ., Dover, DE

Abstract: Human brain pathways mature postnatally with some pathways maturing well into adulthood. Whether an extended postnatal development of pathways is unique to humans is unclear. We have yet to characterize the maturation of pathways in model systems and generate a complete resource to map corresponding postnatal ages across humans and model systems. Mice are the most commonly studied model system for human health. We therefore focused on tracking the maturity of pathways in mice and mapping those findings to humans. We collected developmental time points (n=162) across pre- and postnatal ages in both species, and we generated high resolution diffusion magnetic resonance (MR) tractography scans of the mouse brain (n=18) at postnatal day 3, 4, 12, 21, and 60. We use these data to trace the ontogeny of circuits (e.g., cingulate bundle, olfactory association pathway, corpus callosum). These pathways grow postnatally with some pathways largely ceasing growth shortly after birth, while others grow well through postnatal day 21 to postnatal day 60, which correspond to humans in their first decade. Some white matter pathways mature for an extended duration in mice as they do in humans. More generally, these findings underscore the importance of translational tools to map common biological processes across species.

Disclosures: M. Bryant: None. **K. Ofori:** None. **N. Cottam:** None. **J. Rogge:** None. **J. Sun:** None. **C. Charvet:** None.

Poster

PSTR374: Human Connectomics

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Program #/Poster #: PSTR374.12/Z10

Topic: I.03. Anatomical Methods

Support: NIH SPARC 75N98022C00018

Title: Interconnectivity of the human accessory nerve with nearby cranial nerves at the fascicular level

Authors: S. SCHERER[1], J. VILLAFUERTE[2], S. O'NEILL[3], L. LUNASCO[2], B. BRUNSMAN[2], J. ZHANG[4], J. CHIN[4], Z. SAMBA[5], K. WORKMAN[2], S. BOKHARI[2], A. UPADHYE[6], N. B. NUZOV[4], A. SHOFFSTALL[7], *A. R. CROFTON[7,8];

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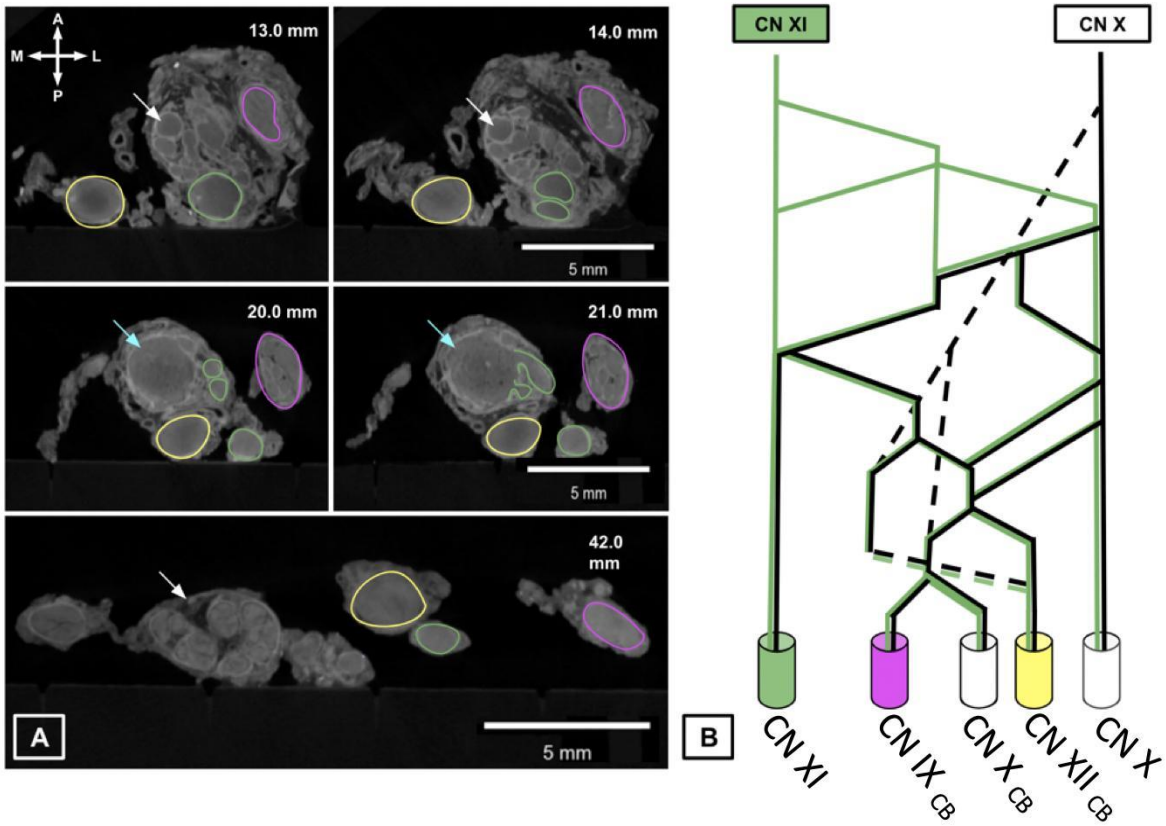
Abstract: Background: Cranial nerve XI (CN XI), the accessory nerve, has cranial and cervical roots that coalesce after exiting the spinal cord and medulla. Intraoperative electrostimulation studies of CN XI cranial roots have elicited vocal cord responses – a function attributed to the vagus nerve (CN X). Gross anatomic studies have shown communicating branches between CNs XI and X as well as spinal nerves C1-C5. To investigate the anatomic basis of these prior findings, we examined the fascicular anatomy of CNs IX-XII. **Methods:** CNs IX-XII were dissected bilaterally in 2 cadavers (n=4 nerve bundles), stained with phosphotungstic acid (3% v/v in deionized water), and imaged via microCT with 11.4 μm voxel resolution. MicroCT images were segmented to track nerve fascicles over a 49 mm distance starting at the caudal margin of the jugular foramen and progressing inferiorly. **Results:** CN XI fascicular merging and splitting events were identified and characterized with respect to the surrounding lower cranial nerves (Figure 1A). Our results reveal four unique intra- and inter-nerve fascicular merging/splitting types. Fascicular exchanges between CN XI with CNs IX, X, and XII are demonstrated (Figure 1B). **Conclusions:** These results suggest that CN XI exchanges fibers with all 3 of the lower cranial nerves, not just CN X, and these communications are not appreciated with gross dissection alone. Such insights into this understudied aspect of neuroanatomy may inform peripheral nerve electrostimulation therapies and reshape understanding of lower cranial nerve innervation patterns.

Figure 1. (**A**) Axial microCT images of CNs IX-XII. Images represent different distances distal to the jugular foramen. (**B**) Schematic representation of anastomoses between CN X and CN XI. Pink border; CN IX = Glossopharyngeal Nerve; White Arrow; CN X = Vagus Nerve; Green Border; CN XI = Accessory Nerve; Yellow Border = Hypoglossal Nerve; Teal Arrow = Nodose Ganglion; CN IX_{CB} = Communicating Branch with Glossopharyngeal Nerve; CN X_{CB} = Communicating Branch with Vagus Nerve; CN XII_{CB} = Communicating Branch with Hypoglossal Nerve.



Disclosures: S. Scherer: None. **J. Villafuerte:** None. **S. O'Neill:** None. **L. Lunasco:** None. **B. Brunsman:** None. **J. Zhang:** None. **J. Chin:** None. **Z. Samba:** None. **K. Workman:** None. **S. Bokhari:** None. **A. Upadhye:** None. **N.B. Nuzov:** None. **A. Shoffstall:** None. **A.R. Crofton:** None.

Poster

PSTR374: Human Connectomics

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Program #/Poster #: PSTR374.13/Z11

Topic: I.03. Anatomical Methods

Support: NIH NIBIB R01EB029272
NIH NIBIB R01EB030896NSF
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NSF BCS 1734853
NSF BCS 1636893
ACI 1916518
IIS 1912270

The Kavli Foundation
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Title: White matter connections shape cortical semantic representations

Authors: *S. GUO[1], B. CARON[2], F. PESTILLI[3], A. G. HUTH[4];
[1]Neurosci., Univ. of Texas at Austin, Austin, TX; [2]Neurosci., The Univ. Of Texas At Austin, Austin, TX; [3]Psychology, The Univ. of Texas at Austin, Austin, TX; [4]The Univ. of Texas at Austin, Austin, TX

Abstract: Long-range myelinated axonal projections constitute the white matter connection between distal computational units in the brain. White matter connections have been studied across subfields of neuroscience and associated with specific cognitive processes both in health and disease. However, studies that focus on specific tasks or lesions also focused primarily on individual white matter tracts or the connectivity across limited regions of the cortex. Therefore, it is difficult to characterize the type of operations that major white matter connections may contribute to cognition and perception. To address this gap, we used semantic stimuli that elicit widespread responses across the cortex under functional neuroimaging (semantic representation mapping; Huth et al., 2016). We also used advanced anatomically-informed tractography (Smith et al., 2012) and segmented 31 major white matter tracts (Hayashi & Caron et al., 2024) for individual brains. After mapping the semantic representations and white matter tract endpoints, we investigated the pattern of semantic representations at the two ends of each white matter tract and compared the similarity within each tract. Our analyses show that (1) similarity in semantic representations within each tract is above chance level, and that (2) semantic representations at the two endpoints of a tract were not identical. Specifically, we show that major white matter tracts such as the commissural tracts and the arcuate fasciculus have similar semantic representations on the two endpoints, whereas the middle and inferior longitudinal fasciculi have extremely different representations on their endpoints. We hypothesize that the change in semantic representations across a tract represents the change in information processing contributed by the tract to support semantic processing.

Disclosures: S. Guo: None. **B. Caron:** None. **F. Pestilli:** None. **A.G. Huth:** None.

Poster

PSTR374: Human Connectomics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.14/Z12

Topic: I.03. Anatomical Methods

Support: NIA R01 AG064247).

Title: Modular architecture of the brain's intrinsic functional networks during periadolescence is associated with cognitive ability: Findings from the PRANK study

Authors: *C. PHIPPS[1], A. HELLER-WIGHT[2], M. K. RAMIREZ[2], J. SEXTON[2], A. WILHELM[2], D. E. WARREN[2];
[1]Univ. of Nebraska Med. Ctr., Omaha, NE; [2]Neurolog. Sci., Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: The human brain is organized into intrinsic functional networks (IFNs). Connectivity between IFNs has been observed to change with development, aging, and disease. During childhood, connectivity between IFNs changes continues to develop through the periadolescent epoch before stabilizing in early adulthood. However, periadolescent IFN connectivity remains underspecified. We are currently conducting an NIA-funded study titled the Polygenic Risk of Alzheimer's disease in Nebraska Kids (PRANK) study (NIA R01 AG064247). Our study seeks to measure the association between an individual's polygenic risk for Alzheimer's disease (AD-PRS) on brain structure, brain function, and cognition in periadolescent children (age 8-13 years). Here we report cross-sectional findings from our study focused on the relationship between brain network measures and cognitive performance from periadolescent children enrolled in the PRANK study (N=160, 81F). Cognitive ability was measured using the NIH Toolbox cognitive battery, and brain measures included both structural and functional MRI. Specifically, cognitive measures included Picture Sequence Memory Test, List Sorting Working Memory Test and Fluid Cognition, Crystallized Cognition, Early Childhood, and Cognitive Function composite scores. A connectomic approach was utilized to characterize the connectivity of the brain's IFNs in the using modularity. Modularity measures the relative strength of within-network connectivity versus between-network connections. In the context of the human brain, modularity of IFNs has been associated with development, aging, and disease. Here, modularity values were calculated from resting-state fMRI data with the Human Connectome Project's Connectome Workbench software and custom Python software using the NetworkX module. We observed statistically significant associations between modularity of the brain's IFNs and performance on the list sorting working memory assessment and the fluid cognitive composite score from the NIH Toolbox cognitive battery. Concretely, Modularity was associated with working memory ability and fluid composite measures of cognition (each $r > 0.15$, $p < 0.05$). This study observed associations between connectivity of the brain's IFNs and cognitive ability during the periadolescent epoch. Future directions include analysis of longitudinal data to identify changes in brain IFN organization and cognitive ability during this developmental epoch, and examination of the effects of AD-PRS on brain and cognitive measures.

Disclosures: C. Phipps: None. **A. Heller-Wight:** None. **M.K. Ramirez:** None. **J. Sexton:** None. **A. Wilhelm:** None. **D.E. Warren:** None.

Poster

PSTR374: Human Connectomics

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Program #/Poster #: PSTR374.15/Z13

Topic: I.03. Anatomical Methods

Support: National Institutes of Health (NIH) OD026585 (LAH)
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National Institutes of Health (NIH) DK027627 (TLP)
National Institutes of Health (NIH) OD028183 (MPW)
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (LAH)

Title: High resolution mapping of small fascicles within the human cervical vagus nerve for guidance and refinement of neural interfaces and protocols for vagus nerve stimulation

Authors: *N. BISCOLA[1], P. BARTMEYER[1], Y. BESHAY[2], P. MIHAYLOV[3], T. POWLEY[4], M. P. WARD[5], L. A. HAVTON[6];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Weldon Sch. of Biomed. Engin., Purdue Univ., West Lafayette, IN; [3]Surgery, Indiana Univ. Sch. of Med., Indianapolis, IN; [4]Psychological Sci., Purdue Univ., West Lafayette, IN; [5]Biomed. Engin., Purdue Univ., West Lafayette, IN; [6]Dept. of Neurol., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Vagus nerve stimulation (VNS) represents an established adjunctive therapy for medication-resistant epilepsy and clinical depression, but current VNS protocols and therapeutics are limited by off-targets effects. Mechanisms underlying treatment effects and adverse effects are also not well understood. This study investigated the fascicular and sub-fascicular organization of the cervical vagus nerve segments of human transplant organ donors (n=27) using a combined light microscopy (LM) and transmission electron microscopy (TEM) approach with digital segmentation of all myelinated and unmyelinated axons. Our recent LM and TEM studies identified small vagal fascicles, which have escaped prior detection by non-invasive diagnostics and LM of frozen and paraffin-embedded sections after trichrome or H&E staining. The small vagal fascicles contributed to a right-sided dominance in the cervical vagus segment in both men and women as well as to a higher number of cervical vagal fascicles in women. Small fascicles were prevalent in both sexes, and, by size distribution, the first quartile included small fascicles with a circumference of less than 300 µm. These fascicles included those with an unprecedented small cross-sectional area and thin perineurium. However, all cervical vagal fascicles, regardless of size, shared common features and exhibited a perineurium, myelinated and unmyelinated axons, collagen fibers within the endoneurium, and Schwann cell nuclei. Based on prior modeling studies, it has been suggested that the smallest fascicles with the thinnest perineurium may be the most likely candidates for early recruitment by VNS. We show extensive heterogeneity with regards to, not only fascicle size, but also the relative composition of small fascicles by myelinated axons of varied sizes and myelination and by unmyelinated axons. Functional predictions of evoked compound nerve action potentials (CNAPs) by a heuristic action potential interpreter (HAPI), with the inclusion of all individual myelinated and unmyelinated axons within each fascicle, suggested physiologic heterogeneity with a broad range of CNAP responses possible among the small cervical fascicles due to their different compositions. Our findings highlight the need for a detailed characterization of the sub-fascicular organization of small fascicles within the human cervical vagus to better predict on-target nerve fiber recruitment and guide new VNS refinement strategies. VNS targeting of select fascicles and fiber populations may help reduce stimulation-related side effects, such as voice changes and coughing, and improve VNS tolerability and therapeutic outcomes.

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Poster

PSTR374: Human Connectomics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.16/Z14

Topic: I.04. Physiological Methods

Support: NIH 5U01NS126050
NIH RM1MH132651

Title: A novel imaging platform for investigating changes in functional connectivity in human-induced pluripotent stem cell neuronal models of neuropsychiatric disease

Authors: H. CHORSI[1], ***Y. JIN**[2], J. MARTIN[3], Y. KAMTE[3], M. F. WELLS[4], B. NOVITCH[5], D. H. GESCHWIND[3], P. GOLSHANI[6], D. AHARONI[7];
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Abstract: Neuropsychiatric disorders (NPDs) such as schizophrenia, bipolar disorder, and autism spectrum disorder represent significant causes of disability, yet their underlying neurobiological mechanisms remain poorly understood. Human-induced pluripotent stem cell (iPSC)-derived neurons present a promising model for bridging the gap between animal models and human pathological conditions, offering novel insights into the genetic landscape of NPDs. However, monitoring and manipulating the activity of identified neurons in culture in a high-throughput manner has not been achievable until now. To bridge this technological gap, we have developed a high-throughput calcium imaging and optogenetic stimulation system, named the multi-well STIMscope (spatiotemporal illumination microscope). This system enables the tracking and manipulation of neuronal activity in multiple wells simultaneously. It integrates miniaturized optics into a compact well-block array capable of independently monitoring up to 20 wells in a standard 96-well plate configuration. The STIMscope features a novel tandem-lens configuration with large-aperture lenses, significantly enhancing light collection efficiency and field of view. Coupled with a real-time central control unit and a GPU-accelerated closed-loop analysis pipeline, the STIMscope enables real-time modulation and monitoring of neural activity. The system has undergone testing and validation using neurons derived from iPSCs. We are capable of simultaneously recording calcium transients in multiple wells. Current experiments involve testing changes in neuronal excitability and synaptic connectivity in neurons engineered with CRISPR-Cas9 technology, incorporating loss-of-function mutations in genes implicated in NPDs. This approach not only deepens our understanding of the complex genetic and cellular mechanisms involved in these disorders but also paves the way for high-throughput drug screening and effective treatments.

Disclosures: H. Chorsi: None. **Y. Jin:** None. **J. Martin:** None. **Y. Kamte:** None. **M.F. Wells:** None. **B. Novitch:** None. **D.H. Geschwind:** None. **P. Golshani:** None. **D. Aharoni:** None.

Poster

PSTR374: Human Connectomics

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR374.17/Z15

Topic: I.04. Physiological Methods

Support: NIH 5U01NS126050
NIH RM1MH132651

Title: The STIMscope: an open-source platform for large field-of-view spatiotemporal imaging and patterned illumination

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Abstract: Large field-of-view (FOV) microscopes play a crucial role in neuroscience by enabling the study of neuronal population imaging across different brain regions. They facilitate the exploration of intricate interactions among neurons within neural networks, offering a broader perspective on brain function and connectivity. However, the development of such microscopes based on traditional microscopy designs has been limited by the high-magnification and high numerical aperture dogma in microscope design. Using advances in CMOS technology to achieve large FOV while maintaining high resolution can create innovative tools that deepen our understanding of complex neurological processes. To address these limitations, we introduce the STIMscope (SpatioTemporal Illumination Microscope), a highly adaptable, large FOV microscope for single-cell resolution fluorescence imaging and optogenetic manipulation in behaving animals, brain tissue slices, and neuronal cultures. The STIMscope is equipped with a back illuminated CMOS image sensor and a Digital Micromirror Device (DMD) to achieve simultaneous neuronal imaging and patterned illumination. The STIMscope platform features a centralized control unit designed to oversee and regulate all its integrated components. This central control facilitates seamless communication among the various parts of the system, ensuring synchronized operation and optimal performance. Furthermore, the STIMscope is equipped with a closed-loop, real-time analysis pipeline that leverages GPU-accelerated computing for processing neural data and generate activity-driven excitation patterns for the DMD unit, allowing for real-time adjustment and optimization based on ongoing data analysis. All these features are integrated into a low-cost (under $5k) and open-source design, making the platform easily accessible and deployable for research laboratories.

To demonstrate the versatility and performance of the STIMscope, we have performed large FOV imaging of visual cortex in freely behaving mice and constructed a tractable “cortical circuit in a dish” experimental setup to investigate the principles of cortical plasticity and computation in organotypic brain cultures.

Disclosures: H. Chorsi: None. **S. Soldado-Magraner:** None. **L. Lu:** None. **Y. Liu:** None. **F. Sangiuliano Jimka:** None. **Y. Dan:** None. **D.V. Buonomano:** None. **D. Aharoni:** None.

Poster

PSTR374: Human Connectomics

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Program #/Poster #: PSTR374.18/Z16

Topic: I.03. Anatomical Methods

Support: NIH Grant U01 MH117023

Title: High-resolution human brain 3D reconstruction with light-sheet fluorescence microscopy

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Abstract: 3D reconstruction of the human brain at high resolution is one of the most important challenges of neuroscience. However, a detailed map of the anatomical disposition of neurons, obtained by volumetric imaging is still lacking. A complete atlas would be an important step for deeply understanding the brain function, providing anatomical information useful to decipher the neuronal pattern in healthy and diseased conditions. To this aim, we developed a new clearing method named SHORT that in combination with an advanced double-view light-sheet fluorescence microscope (LSFM) and an automated machine-learning based images analysis allow to perform volumetric study of the human brain. We applied our methodology to the Broca’s area, obtaining the neuronal distribution analysis of block of 4 x 4 x 2 cm^3. In particular, we cut the block in 400-µm thick slices that were cleared and labeled with four different markers: NeuN, SST (somatostatin) and CR (calretinin) for neuronal characterization, and DAPI for nuclei labelling. Subsequently, we performed the acquisition with LSFM obtaining images with a resolution of 3,6 µm isotopically. The post-processing analysis allowed to obtain the neuronal counting through the whole block. The work presented here demonstrates the possibility of obtaining a fast 3D reconstruction of the human brain at high-resolution, paving the way to the possibility of finally mapping a comprehensive atlas of the human brain.

Disclosures: F.S. Pavone: None. **J. Ramazzotti:** None. **N. Brady:** None. **M. Scardigli:** None. **C. Checcucci:** None. **F. Cheli:** None. **F. Castelli:** None. **M. Sorelli:** None. **D. Di Meo:** None. **G. Mazzamuto:** None. **L. Silvestri:** None. **P. Frasconi:** None. **I. Costantini:** None.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.01/Z17

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: 1R61NS118651-01A1

Title: Insights Into Depression in Chronic Pain: An Exploration of EEG-Based Biomarkers

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Abstract: Background: Previous studies have indicated that chronic pain is highly comorbid with other disorders such as depression. Depression in chronic pain is associated with worsening clinical profiles including worse pain and poorer functioning. However, the pathophysiological mechanisms underlying depression in chronic pain remain unidentified. In response, we sought to identify EEG based biomarkers of depression in chronic musculoskeletal pain patients (MSK). Methods: 10 minutes of resting state EEG with eyes closed was recorded in 137 MSK patients who were primarily Non-Hispanic White (Mage = 56.58 years old, SD = 15.14; 76% Female) using 64 Ag-AgCl HydroCel Geodesic Sensor Nets. EEG data were preprocessed. Cortical bioelectrical generators corresponding to scalp EEG were modelled using equivalent current dipoles and stratified using affinity propagation. Depression symptoms over the past week were assessed at the study visit using the PROMIS® Depression Short Form. This questionnaire employs a T-score system, benchmarked against the US population with a mean of 50 and a standard deviation of 10. Elevated T-scores suggest heightened levels of depression. A T-score of 65 was utilized to discern comparison groups (I.e., 65 ≤ Low Depression; 65 > High Depression). All procedures were approved by Stanford University's IRB. Results: 15 clusters were revealed (1 Parent and 14 subclusters). The cluster of dipoles located broadly in the left occipital lobe with a centroid likely in the fusiform gyrus, with greatest differences seen in between approximately 2Hz-30Hz. In essence, those with High Depression showed greater alpha and beta peaks as well as an increase in aperiodic EEG activity from the left occipital lobe. Discussion: Our findings align with previous studies pointing to functional changes in the occipital lobe in depression and suggest that EEG based biomarkers that have previously been detected in depressed patients may be found in chronic pain patients with depression. These findings provide a framework for future research exploring the role of EEG biomarkers to further understand depression in chronic pain patients.

Disclosures: C.B. Orsini: A. Employment/Salary (full or part-time):; Stanford University. **C. Konstantopoulos:** A. Employment/Salary (full or part-time):; Stanford University. **K.N. Bornhoft:** A. Employment/Salary (full or part-time):; Stanford University. **E. Lannon:** A. Employment/Salary (full or part-time):; Stanford University. **S. Mackey:** A. Employment/Salary (full or part-time):; Stanford University.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.02/Z18

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Standardized pharmaco-sleep-electroencephalography as a preclinical tool for antidepressant drug profiling

Authors: C. ALLIOUX, M. VILLALBA, C. DUMONT, B. CARABALLO, E. GRONLIER, D. DARANKOUM, ***H. MONCHAL**, C. ROUCARD, Y. ROCHE, J. VOLLE, C. HABERMACHER;
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Abstract: The growing understanding of underlying mechanisms of depression, a multifactorial mood disorder with substantial global prevalence, promoted advancements in antidepressant drug development. Nevertheless, the industry has persistently encountered challenges during the early stages of clinical development. Pharmaco-electroencephalography (pharmaco-EEG) from freely moving animals, a widely used translational tool, holds significant potential to inform early decision-making regarding a compound's likelihood of clinical success. However, changes in vigilance states (VS) are the most prominent confounding variable in EEG animal studies and alteration of sleep-waking behavior may be a relevant characteristic *per se*, leading to state-dependent pharmaco-EEG profiling. Because of the lack of consensus and general guidelines in this type of experiments, discrepancies are often observed.
In this study, we hypothesized that drug-effects may be expressed differently depending on the VS during recording sessions and proposed automatic state-detection (machine learning approach) as a viable tool for estimating drug state-induced effects. We evaluated the possibility to employ this method to assess the dose-dependency of antidepressants, with distinct mechanisms of action (MOA): fluoxetine and maprotiline (at 2 to 20mg/kg and 2.5 to 20 mg/kg, respectively). The experiments were carried out in wild-type C57BL/6 mice with chronically implanted electrodes. Pharmaco-EEG analysis revealed consistent effects across the two antidepressants: a dose-dependent reduction in absolute power across various spectral bands with certain effects showing structure-specific characteristics. Despite this overall consistency, differences were observed in specific bands among the treatments. As an illustration, maprotiline induced an increase of absolute power of delta and theta bands in parietal and prefrontal cortices while fluoxetine decreased the absolute power of those bands. Fluoxetine impacted brain structures differently within the high frequencies range: the observed decrease affected

specifically the parietal cortex. State-specific analyses of maprotiline, on the other hand, showed that the effects seen on total data was largely driven by the induced sedation.
These findings support the establishment of pharmaco-EEG "signatures" that are not only specific to the class of compounds but also reflective of their distinct MOA. This state-specific analysis facilitated discovery of state-dependent drug-effects. This may ultimately lead to better cross-species translation of electrophysiological effects of pharmacological modulations.

Disclosures: C. Allioux: A. Employment/Salary (full or part-time):; SynapCell. **M. Villalba:** A. Employment/Salary (full or part-time):; SynapCell. **C. Dumont:** A. Employment/Salary (full or part-time):; SynapCell. **B. Caraballo:** A. Employment/Salary (full or part-time):; SynapCell. **E. Gronlier:** A. Employment/Salary (full or part-time):; SynapCell. **D. Darankoum:** A. Employment/Salary (full or part-time):; SynapCell. **H. Monchal:** A. Employment/Salary (full or part-time):; SynapCell. **C. Roucard:** A. Employment/Salary (full or part-time):; SynapCell. **Y. Roche:** A. Employment/Salary (full or part-time):; SynapCell. **J. Volle:** A. Employment/Salary (full or part-time):; SynapCell. **C. Habermacher:** A. Employment/Salary (full or part-time):; SynapCell.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.03/Z19

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support:
National Science and Technology Council, Taiwan: NSTC 112-2321-B-A49-021
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Dr. Albert C. Yang was supported by he Ministry of Education (Aim for the Top University Plan), Taipei, Taiwan

Title: Region-specific brain age analysis in bipolar and major depressive disorders using T1-weighted MRI

Authors: *J.-D. ZHU[1], A.-C. YANG[1,2,3,4];
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Abstract: Background: The development of artificial intelligence and neuroimaging has facilitated the creation of a brain-age prediction approach, which is increasingly being applied in the study of neuropsychiatric disorders. This study aimed to construct brain-age prediction models for various brain regions using T1-weighted MRI. Subsequently, these models were applied to examine the effects of bipolar disorder (BD) and major depressive disorder (MDD) on deviations in aging trajectories across different brain regions. **Methods:** Brain-age prediction models were constructed using T1-weighted MRI data from a training dataset of 230 normal controls (NCs). Additionally, the study included data from 110 individuals with BD, 68 with MDD, and an independent dataset of 110 NCs. After image preprocessing, we obtained 90 gray matter maps for each participant. We constructed 90 region-specific models based on the training dataset using the Gaussian process regression. These models were applied to the BD, MDD, and NC datasets to predict their brain age and calculate their brain age gap. ANCOVA was used to test the differences in brain age gap between the BD and NC groups and the MDD and NC groups, respectively. **Results:** In the BD group, our results showed significantly accelerated aging in 66 out of 90 gray matter regions. The top ten brain regions most affected by abnormal aging included the bilateral caudate nucleus, left thalamus, right gyrus rectus, left supplementary motor area, right thalamus, left olfactory cortex, left superior frontal gyrus (medial orbital), left superior frontal gyrus (medial), and left Heschl's gyrus. In the MDD group, the results revealed significantly accelerated aging in 67 gray matter regions. The top ten most affected brain regions included bilateral superior frontal gyrus (medial orbital), left superior temporal gyrus, bilateral gyrus rectus, left olfactory cortex, right Heschl's gyrus, right thalamus, left superior frontal gyrus (medial), and temporal pole of left superior temporal gyrus. **Conclusion:** Our results revealed both common and distinct brain characteristics among the participants. Accelerated aging was detected in specific brain regions across different affective disorders, suggesting the potential common neuropathological underpinnings. Concurrently, each disorder showed unique patterns of decline in specific areas, which might reflect their distinct clinical features. These findings are important for deepening our understanding of the pathophysiology and developing more personalized and effective treatment strategies for these disorders.

Disclosures: J. Zhu: None. **A. Yang:** None.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.04/Z20

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: National Science and Technology Council, Taiwan: NSTC 112-2321-B-A49-021
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Dr. Albert C. Yang was supported by the Mt. Jade Young Scholarship Award from the Ministry of Education, Taiwan
Dr. Albert C. Yang was supported by Brain Research Center, National Yang Ming Chiao Tung University
Dr. Albert C. Yang was supported by he Ministry of Education (Aim for the Top University Plan), Taipei, Taiwan

Title: The impact of white matter hyperintensities in bipolar disorder subtypes and major depressive disorder

Authors: *H. LEE[1], A.-C. YANG[1,2,3,4];
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Abstract: White matter hyperintensities (WMHs) are common features in brain imaging of vascular diseases and are associated with conditions such as stroke, cognitive decline, and mental disorders. WMHs manifest as high signal intensity on T2-weighted images (T2WI) and are linked to the local water content in the brain's white matter. Past studies have noted the frequent occurrence of WMHs in bipolar disorder (BD), while the association between major depressive disorder (MDD) and WMHs is more pronounced in early-onset depression and late-life depression. When studying the relationship between changes in white matter hyperintensities (WMHs) and affective disorders, researchers often face limitations due to sparse data on bipolar disorder (BD) subtypes. Moreover,there's been relatively little investigation into the distinctions between BD subtypes and major depressive disorder (MDD) in adult populations. Therefore,exploring the association of WMH changes among BD subtypes and MDD within the same age group becomes crucial. This research aims to investigate the WMHs as the biomarker for distinguishing between BD subtypes and MDD,offering an imaging indicator distinct from traditional structural and functional imaging. Therefore, the objective is to analyze the volume of WMHs to differentiate between BD subtypes and MDD patients. T2WI images of 55 BD-I,55 BD-II, and 199 MDD patients were analyzed using data from the UK Biobank database. Each patient’s images were coregistered to the MNI-152 standard space and segmented for WMH volume using the SPM LST toolbox. After removing extreme values beyond three standard deviations and standardizing the data, the analysis was conducted on 55 BD-I, 47 BD-II, and 194 MDD patients using one-way ANOVA with post-hoc analysis. Results indicated that the WMH volume in BD-I was significantly greater than that in the MDD group, and similarly, the WMH volume in BD-II was also significantly greater than that in the MDD group. The volume in the BD-I group was more than three times larger than that in the MDD group, and the volume in the

BD-II group was also more than 2.5 times larger than that in the MDD group. In summary, these findings suggest that the WMH volume in BD subtypes is significantly greater than in MDD patients. In future studies, we plan to incorporate the location of WMH to generate WMH frequency maps and conduct comparative analyses with healthy control groups.

Disclosures: H. Lee: None. **A. Yang:** None.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.05/Z21

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Mapping metabolomic alteration in search of consistent signature biomarker for depression through comparative analysis

Authors: *P. SINGH[1], A. K. DATUSALIA[2];
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Abstract: "Mapping metabolomic alteration in search of consistent signature biomarker for depression through comparative analysis"**Pooja Singh, Ashok K. Datusalia****Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER) Raebareli, (U.P), Lucknow-226002, India chauhan.poojagwl@gmail.com*Depression is a complex and multifaceted disorder with underlying metabolic perturbations that remain inadequately understood. Despite numerous studies exploring metabolite profiles post-pharmacological interventions, a quantitative understanding of consistently altered metabolites not yet established. This study aims to bridge this gap by identifying metabolites exhibiting consistent changes in extensive metabolomic investigations of depressive subjects.Our comprehensive analysis involved a meticulous vote counting approach, binomial distribution and network analysis focusing on dysregulated metabolites consistently exhibiting upregulation or downregulation across brain, blood, and urine samples in depression subjects as well as animal models mimicking depressive conditions. The dataset comprised 18,164 differential metabolites extracted from a total of 1,018 metabolic studies, encompassing a diverse range of animal and human subjects.The findings of this study shed light on the metabolic signatures that transcend species and biological compartments, providing a robust foundation for understanding the metabolic intricacies of depression. Notably, our analysis identified 11 (1.3%) metabolites common in the brain, 65 (6.1%) in blood, and 9 (2.9%) in urine, shared across species which are human, rat, and mice models. These shared metabolites underscore potential conserved pathways and mechanisms implicated in depressive conditions across species. By identifying consistently altered metabolites, we aim to contribute to the development of diagnostic biomarkers and

targeted therapeutic interventions for depressive disorders.**Keywords:** Depression, Metabolomics, Human and Animal Models, Comprehensive Analysis, Biomarkers

Disclosures: P. Singh: None. **A.K. Datusalia:** None.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.06/Z22

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: A preclinical platform for phenotypic characterization of natural products in iPSC-derived and primary neuronal models

Authors: M. A. CARRASCO, **A. MARKOWITZ**, A. LOBO, A. PERRIS, *S. BERKOVITCH, J. M. BROWN;
Sensorium Therapeut., Boston, MA

Abstract: Sensorium leverages the intersection of human experience, human biological systems, and machine learning to identify and develop novel pharmacology and chemistries to treat neuropsychiatric and neurological disease and alleviate human suffering. Our AI-driven Product Engine identifies natural products based on evidence of human use, providing an enriched discovery set for investigation. Here, we describe our preclinical platform, which provides a phenotypic "fingerprint" to guide our characterization of compounds discovered through our Product Engine. We illustrate the development of assays for neuronal signaling and synaptic activity in iPSC-derived and primary models which we use to characterize reference and comparator compounds with known activities. Finally, we highlight key examples of relevant findings when we apply our platform to our discovery set of natural products.

Disclosures: M.A. Carrasco: A. Employment/Salary (full or part-time):; Sensorium Therapeutics. **A. Markowitz:** A. Employment/Salary (full or part-time):; Sensorium Therapeutics. **A. Lobo:** A. Employment/Salary (full or part-time):; Sensorium Therapeutics. **A. Perris:** A. Employment/Salary (full or part-time):; Sensorium Therapeutics. **S. Berkovitch:** A. Employment/Salary (full or part-time):; Sensorium Therapeutics. **J.M. Brown:** A. Employment/Salary (full or part-time):; Sensorium Therapeutics.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.07/Z23

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Preclinical neurobehavioral profiling of antipsychotics through miniscope calcium imaging

Authors: *S. HUANG, D. CHENG, L. BELLIER, O. H. MILLER, J. J. NASSI;
Inscopix, Inc, Mountain View, CA

Abstract: Despite the development of numerous antipsychotic drugs to block D2 receptors (D2R), many have proven ineffective in treating patients with schizophrenia. Moreover, existing antipsychotics display varying D2R affinities and interact with multiple neurotransmitter receptors, resulting in inconsistent efficacy and a range of unwanted side effects. Conventional preclinical efficacy assessments, relying on coarse behavioral assessments, lack the sensitivity to distinguish different mechanisms of action and have proven to be poor predictors of clinical performance. The miniscope imaging platform offers a potential solution by enabling cellular-resolution activity measurements of genetically defined neurons in freely behaving animals. This technology provides comprehensive insights into neurobehavioral responses to drugs, promising more sensitive preclinical evaluations.
Here, we aim to demonstrate proof-of-concept by leveraging Inscopix nVista miniscopes and genetically encoded calcium sensors (GCaMPs) to record from thousands of D1R- and D2R-expressing medium spiny neurons (MSNs) in the dorsal striatum, an affected brain region in schizophrenia. Neural activity imaging was synchronized with recordings of animals' locomotor activity in an open field chamber to characterize the neurobehavioral phenotype of phencyclidine (PCP)-induced psychosis. We then investigated the impact of pharmacological interventions using various doses of Haloperidol, a first-generation or typical antipsychotic, on MSNs during periods of rest or movement under both basal and PCP conditions.
Our analysis revealed a spectrum of neural and behavioral abnormalities associated with PCP compared to the control condition. Haloperidol effectively normalized PCP-induced hyperlocomotion, partially recovered neuronal modulation of D2-MSNs during movement but failed to attenuate the PCP-induced abnormalities in D1-MSNs. We went on to apply a similar approach to characterize Clozapine, a second-generation or atypical antipsychotic, and Xanomeline, an M1/M4 agonist currently in late-stage clinical trials. All three drugs tested had distinct neurobehavioral profiles. These multidimensional neurobehavioral profiles offer higher sensitivity for differentiating mechanism of action than behavior alone and should ultimately facilitate the development of more effective and better-tolerated treatments for schizophrenia.

Disclosures: S. Huang: A. Employment/Salary (full or part-time):; Inscopix, Inc. **D. Cheng:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **L. Bellier:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **O.H. Miller:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **J.J. Nassi:** A. Employment/Salary (full or part-time):; Inscopix, Inc.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.08/Z24

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Commonwealth Government: Prioritising Mental Health – Research

Title: Resting State Electroencephalography Complexity is Associated with Oral Ketamine Treatment Response: A Bayesian Analysis of Lempel-Ziv Complexity and Multi-Scale Entropy

Authors: *J. MITCHELL[1], T. ANIJÄRV[2], D. F. HERMENS[3], J. LAGOPOULOS[4]; [1]Thompson Institute, The Univ. of the Sunshine Coast, Sunshine Coast, Australia; [2]Dept. of Clin. Sciences, Malmö, Clin. Memory Res. Unit, Dept. of Clin. Sciences, Malmö, Lund University, Sweden, Lund, Sweden; [3]Thompson Institute, Univ. of the Sunshine Coast, Sunshine Coast, Australia; [4]Thompson Brain and Mind Healthcare, Sunshine Coast, Australia

Abstract: Sub-anaesthetic doses of ketamine are a promising novel treatment for suicidality, however, the evidence for prognostic biomarkers is sparse. Recently, measures of complexity, including Lempel-Ziv Complexity (LZC) and Multi-Scale Entropy (MSE), have been implicated in ketamine's therapeutic action. We evaluated electroencephalogram (EEG)-derived LZC and MSE differences between responders and non-responders to oral ketamine treatment. Thirty-one participants (mean age = 45.64 (SD = 13.95); 54% female) received six single, weekly (titrated) doses of oral racemic ketamine (0.5-3 mg/kg) and underwent EEG scans at baseline (week 0), post-treatment (week 6), and follow up (week 10). Resting state (eyes closed and open) recordings were processed in EEGLAB, and complexity metrics were extracted using the Neurokit2 package. Participants were designated responders or non-responders by clinical response (Beck Suicide Scale (BSS) score reduction of ≥ 50% from baseline to the respective timepoint or score ≤ 6) and then compared in terms of complexity across task types and time. Employing a Bayesian mixed effects model with timepoint, task, and response status as fixed effects and by-participant random effects (random intercepts and slopes). For LZC, there was evidence for a main effect of task, with higher eyes open compared to eyes closed values across timepoints and response status. Similarly, higher MSE values were observed in the eyes open condition for scales 1-4, with the opposite observed from scales 6-10. Averaged over channels (global level), responders displayed elevated eyes open baseline complexity (LZC and MSE scales 1-4) compared to non-responders, with these values decreased at post-treatment (6-weeks) and follow-up (10-weeks;) in responders only. Exploratory Bayesian analyses revealed the elevated baseline eyes-open LZC in oral ketamine responders was not reflective of a global increase in entropy, rather it was spatially localised to the left frontal lobe (electrodes F1, AF3, FC1, F3). This is the first evidence showing EEG-complexity metrics may be sensitive biomarkers for evaluating and predicting oral-ketamine treatment response, and highlights the left pre-frontal cortex as a key region implicated in response among individuals living with chronic suicidality and depression.

Disclosures: J. Mitchell: A. Employment/Salary (full or part-time):; Australian Government Research Training Program Scholarship. **T. Anijärv:** None. **D.F. Hermens:** A. Employment/Salary (full or part-time):; Thompson Institute, Professor of Youth Mental Health and Neurobiology. **J. Lagopoulos:** None.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.09/Z25

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Taipei Veterans General Hospital V113C-144
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Title: Application of fMRI-guided repetitive transcranial magnetic stimulation in the treatment of schizophrenia: a randomized pilot study

Authors: *H.-Y. HSU[1,4], A.-C. YANG[1,2,3,4];
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Abstract: *Background:* Schizophrenia is an intricate psychiatric disorder characterized by positive, negative, and cognitive symptoms. Previous research has indicated that these symptoms may arise from disconnection within brain networks. Over the past few decades, repetitive transcranial magnetic stimulation (rTMS) has been used in schizophrenia. However, the results of rTMS intervention remain inconsistent. Therefore, it is essential to pinpoint an appropriate stimulation target to enhance the effectiveness of rTMS treatment. The current study aims to identify an efficacious stimulation target and explore the outcomes and feasibility of fMRI-guided rTMS in individuals with schizophrenia. *Methods:* Our study included individuals with schizophrenia from Taipei Veterans General Hospital, 8 patients treated with traditional targeting of the left dorsal lateral prefrontal cortex (DLPFC; age: 35.88 ± 8.81; 62.5% in females), and 9 patients with fMRI-guided targeting of the left parietal lobule (P3; age: 29.11 ± 6.60; 44.4% in females). Each participant underwent 10 sessions of rTMS treatment, lasting 30 minutes per day. The DLPFC group received high frequency of 10Hz-rTMS, while the P3 group received low frequency of 1Hz-rTMS. The multidomain symptoms of schizophrenia were assessed using positive and negative symptom scales, Beck's Depression Inventory, Hamilton Depression Rating Scale, Wisconsin Card Sorting Test, and Mini-Mental Status Examination before and

after treatment. *Results:* After receiving 10 sessions of rTMS, overall symptoms ameliorate in two groups. Notably, the P3 group exhibited a significant reduction in positive symptoms compared to the DLPFC group. Additionally, subjective and objective depressive symptoms markedly improved in the P3 groups. Furthermore, cognitive performance in the DLPFC group significantly enhanced following rTMS treatment. *Conclusions:* Our study demonstrates the potential efficacy of fMRI-guided rTMS as a treatment modality for individuals with schizophrenia. We observed significant improvements in overall symptoms by targeting the left parietal lobule. These findings suggest that identifying appropriate stimulation targets through fMRI guidance can enhance the effectiveness of rTMS intervention in schizophrenia.

Disclosures: H. Hsu: None. **A. Yang:** None.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.10/Z26

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Stanley Medical Research Institute grants 03-484 and 06T-797
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Contract # HHSN-271- 2013-00017-C and HHSN- 271-2018-00023-C (NIMH - PDSP)

Title: Presence of proton sensing GPCR modulators in plants used to treat mental disorders in Peruvian traditional medicine

Authors: *C. GALLO[1], G. POLETTI[1], R. ROJAS[1], J. ALBAN[2], A. J. VAISBERG[1];
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Abstract: The family of proton-sensing G-protein coupled receptors (GPCRs) consists of four members that belong to the class A orphan GPCRs: GPR4, GPR65 (TDAG8), GPR68 (OGR1), and GPR132 (G2A). These receptors are expressed ubiquitously, including brain. It is known that all four receptors contribute to different aspects of tumor biology, cardiovascular physiology, and asthma. Recently, some of them have also been involved in mechanosensation, intestinal inflammation, onco-immunological interactions, hematopoiesis, as well as in inflammatory and neuropathic pain. However, their potential role in the modulation of behavior has not been deeply addressed yet. Isolated reports in the past years indicate that at least GPR65 and GPR68 could have a role in the molecular mechanisms of depression and anxiety. Ethanol extracts (n=477) from plant collections corresponding to 265 species from 87 different plant families were tested in functional assays for GPR4, GPR65, GPR68 and GPR132 thanks to the NIMH Psychoactive Drug Screening Program (PDSP) - University of North Carolina, Chapel Hill (UNC). The repository of ethanol extracts was generated through the collection of

information on the traditional use of plants for the treatment of brain disorders in several Peruvian localities and geographical regions. A total of 43 of the assayed extracts (9%) showed action on the four receptors, considering 20% or higher change from basal. A total of 66 (14%) showed action on two or three receptors, considering 50% or higher change from basal. The main traditional uses reported for these extracts are: for nerves/madness, for depression/sadness/ tiredness/cheering up/getting vigorous, for insomnia/ tranquilizer/sedative/anxiety/stress, for headaches. Our plant extracts are an important source of novel molecules active on proton sensing GPCRs which could turn out into a helpful tool to better understand the biology of mental disorders, and merit additional studies.

Disclosures: C. Gallo: None. **G. Poletti:** None. **R. Rojas:** None. **J. Alban:** None. **A.J. Vaisberg:** None.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.11/Z27

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Serotonergic modulation of neuroplasticity in humans: dose dependency and mechanisms

Authors: L. MELO, E. GHANAVATI, ***M.-F. KUO**, M. A. NITSCHE;
IfADo, Dortmund, Germany

Abstract: Studies in animals and humans have shown that cortical neuroplasticity can be modulated by increasing serotonin levels by administering selective serotonin reuptake inhibitors (SSRI). However, little is known about the mechanistic background, especially the contribution of intracortical inhibition and facilitation, which depend on gamma-aminobutyric acid (GABA) and glutamate. The aim of this study is to explore the relevance of drivers of plasticity (glutamate- and GABA-dependent processes) for the effects of serotonin enhancement on tDCS-induced plasticity in healthy humans. A crossover, partially double-blinded, randomized, and sham-controlled study was conducted in 16 healthy right-handed individuals. In each of the 7 sessions, plasticity was induced via transcranial direct current stimulation (tDCS). Anodal, cathodal, and sham tDCS were applied to the left motor cortex under SSRI (20mg / 40mg citalopram) or placebo. Short-interval cortical inhibition (SICI) and intracortical facilitation (ICF) were monitored by paired-pulse transcranial magnetic stimulation for 5-6 hours after intervention. Under placebo, anodal tDCS-induced LTP-like plasticity decreased SICI and increased ICF. In contrast, cathodal tDCS-elicited LTD-like plasticity induced the opposite effect. Under 20 mg and 40 mg citalopram, anodal tDCS did not affect SICI significantly, while ICF was enhanced and prolonged. For cathodal tDCS, citalopram converted the increase of SICI and decrease of ICF into antagonistic effects, and this effect was dosage-dependent since it lasted longer under 40mg when compared to 20mg. We speculate that the main effects of acute

serotonergic enhancement on tDCS-induced plasticity is the increase and prolongation of LTP-like plasticity effects, which involves mainly the glutamatergic system.

Disclosures: L. Melo: None. **E. ghanavati:** None. **M. Kuo:** None. **M.A. Nitsche:** F. Consulting Fees (e.g., advisory boards); Neuroelectrics.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.12/Z28

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: "BANDO RICERCA TRASLAZIONALE" (Dept. Neuroscience, Univ. Turin) grant to Alessandro Vercelli and Paola Rocca

Title: The biological effects of "green-therapy" on Major Depressive Disorder

Authors: *G. PAVARINO[1], C. BRASSO[2], R. SCHELLINO[1], A. CARLUCCIO[2], F. CIRULLI[3], M. M. BOIDO[1], P. ROCCA[2], A. E. VERCELLI[1];
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Abstract: In recent years, human-nature interactions are becoming a fundamental issue. Indeed, spending time in nature reduces stress and promotes mental well-being; however, the underlying biological mechanisms of action are still elusive. Major Depressive Disorder (MDD), one of the most prevalent and debilitating psychiatric diseases, is characterized by severe symptoms that negatively influence health perception and quality of life. Unfortunately, even after antidepressant treatments, a high percentage of patients do not achieve a full recovery. Therefore, to investigate possible combinatorial approaches, we decided to i) evaluate the biological, molecular and epigenetic impact of spending time in the greenery on MDD patients, and ii) highlight the importance of urban "green-therapy" on depressive symptoms. To this aim, we have currently enrolled 32 healthy control subjects (HCS) and 45 MDD out-/in-patients (aged 18-65) randomized into 2 groups: i) one practicing at least 40 min walk, 3-4 days/week, in urban parks; ii) the other not spending time in nature. Patients underwent baseline assessment (T0), then at 1 (T1) and 6 months (T2), while HCS have a single assessment at T0: the evaluation included a psychiatric interview along with a venous blood draw from which we evaluated serological and epigenetic inflammation markers correlating with MDD. Our results in MDD patients, over time (from T0 to T2) after "green-therapy", clearly showed that: i) IL-6 level (normally high in MDD) significantly decreased returning to HCS levels; as well as those of C-Reactive Protein, procalcitonin, leptin, adiponectin and complement C4, even if still not

significantly; ii) the expression of the tested miRNAs (i.e. miRNA-145-3p, miRNA-124-3p, miRNA-132-3p, miRNA-16-5p, miRNA-18a-5p, miRNA-135a-5p) was completely restored in peripheral blood mononuclear cells (PBMCs) and serum, even if still not significantly; iii) the level of the analysed post-translationally modified histone proteins (i.e. H3K9ac, H3K14ac) were significantly restored in PBMCs. These preliminary data provide new scientific evidence about beneficial effects of green environment on depressive symptoms, and propose greenness-related activities as a potential combinatorial treatment to reduce pharmacological administration and achieve a personal full recovery.

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Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.13/Z29

Topic: H.13. Schizophrenia

Support: NIH Grant MH-094268 Silvio O. Conte center

Title: The molecular and cellular impact of relapse, a key determinant of poor prognosis of schizophrenia and psychotic disorders

Authors: S. WU, *K. ISHIZUKA, A. HAYASHIDA, K. YANG, A. SAWA;
Johns Hopkins Univ., Baltimore, MD

Abstract: Schizophrenia (SZ) is a highly debilitating mental disorder that imposes substantial economic burdens. One of the major determinants of poor prognosis is the occurrence of psychotic exacerbation, often termed “relapse”. The prevalence of relapse in SZ patients is estimated to be around 35-54 % at 1.5-2 years of follow-up. Thus, combating relapse should be a central goal in the treatment of SZ. Nevertheless, due to lack of molecular/cellular signatures and mechanism associated with relapse at least at present, no major progress in the development of treatment has been made thus far. By using a longitudinal cohort of patients with early-stage psychosis and biopsied olfactory neuronal cells (ONCs) from these patients, we have investigated neuron-relevant molecular/cellular signatures after relapse, in association with clinical and brain imaging phenotypes. We recently reported altered connectivity in the relapse group compared with the non-relapse group through a resting state-functional MRI (rs-fMRI) study. Utilizing the same dataset from 31 relapse patients and 54 non-relapse patients, we have conducted further analysis and observed widespread (non-region-specific, brain-wide) increases in functional connectivity in the relapse group compared to the non-relapse group. In parallel, we have conducted RNA-seq analysis from ONCs of 29 relapse patients and 32 non-relapse patients from the same cohort. Pathway analysis adjusting for age, sex, race, tobacco use, duration of illness, antipsychotics, and surrogate variables identified two significant pathways, including the

calcium signaling pathway with the utmost statistical significance. We have also examined stimulus-dependent Ca^{2+} kinetics elicited by adenosine triphosphate (ATP) in ONCs and observed significantly steeper Ca^{2+} slopes and greater peak amplitudes in response to ATP in the relapse group compared to the non-relapse group. Based on the collected data, we hypothesized that relapse affects calcium signaling in neurons, which in turn alters brain functional connectivity. By increasing the sample size, we are testing this hypothesis with the hope that the modulation of calcium signaling may offer a promising avenue for mitigating the adverse brain changes associated with relapse.

Disclosures: S. Wu: None. **K. Ishizuka:** None. **A. Hayashida:** None. **K. Yang:** None. **A. Sawa:** None.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.14/Z30

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Association between readiness potential and serum neurofilament-light protein in schizophrenia patients.

Authors: *N. ZAMAN, JR[1], B. NARASIMHA RAO[2], M. GOYAL[3], S. MISHRA[4], A. PARMAR[4];
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Abstract: Title: Association between Readiness Potential and Serum Neurofilament-Light Protein in Schizophrenia Patients. Background: This study was designed to explore the association between readiness potential (RP) and serum levels of neurofilament light chain protein (NfL) in schizophrenia (SCZ) patients. Schizophrenia is a progressive degenerative disorder characterized by self-disorders (SD) and cognitive decline. Understanding the neurobiological underpinnings of SCZ is crucial for diagnostic and prognostic purposes. RP is a neurophysiological marker reflecting preparedness for self-generated movements, and NfL is as a biomarker for neuro-axonal damage and progression of disease. **Methods:** A cross-sectional observational exploratory study was conducted between December 2022- December 2023 involving 24 (19 males: 5 females) SCZ patients (recruited from Department of Psychiatry, All India Institute of Medical sciences (AIIMS), Bhubaneswar) and 25 (20 males :5 females) healthy controls (HC). Intensity of symptoms were evaluated using *Positive and Negative Syndrome Scale* (PANSS) and a part of *Examination of Anomalous Self-Experience* (EASE). RP parameters, including amplitude, slope, and area under the curve, were measured using electroencephalography (EEG) in Fz, Cz, Pz, C3 and C4. Serum samples were collected to

measure NfL levels using *Single Molecular Assay* (SIMOA). Cognitive processing speed was assessed using *Digit Symbol Substitution Test* (DSST). Correlation analyses were performed to assess the relationship between RP parameters, NfL levels, and clinical features of SCZ. **Results:** SCZ patients showed significant reductions in Cz in maximum peak amplitude (p=0.0056), slope (p=0.0004), and area under the curve (p=0.0024) of RP. Similar significant reductions were found in other electrode sites as well. Additionally, SCZ patients showed elevated NfL levels (p=0.0362), suggesting potential neuronal damage or neuro-axonal loss. DSST score was significantly reduced in SCZ (p=0.0002). Correlation analyses revealed associations between RP parameters and EASE-2 in SCZ (r=-0.5592, p=0.0045) emphasizing the disruption of motor preparedness in SCZ. However, no correlation was found between RP parameters and NfL levels in SCZ probably due to small sample size. **Conclusion:** Reduction in RP and elevated NfL levels may be considered as potential biomarkers of self-disorders and neurodegeneration and progression of in SCZ, respectively. **Conflicts of interest:** There are no conflicts of interest. Note: The work was conducted after institutional (AIIMS, Bhubaneswar) ethical clearance.

Disclosures: N. Zaman: None. **B. Narasimha Rao:** None. **M. Goyal:** None. **S. Mishra:** None. **A. Parmar:** None.

Poster

PSTR375: Biomarkers and Therapeutics in Affective Disorders and Schizophrenia

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR375.15/Z31

Topic: A.07. Developmental Disorders

Support: TRIUMPH Initiative Funding

Title: Relationship between Dopamine Transporter Binding Abnormalities, Amygdalar Functional Connectivity, and Camouflaging in Individuals with Autism Spectrum Disorder

Authors: *N. NURAINI[1], C. APPLING[1], B. FERGUSON[2], D. Q. BEVERSDORF[3]; [1]Univ. of Missouri, Columbia, MO; [2]Univ. of Missouri Thompson Ctr. For Autism, Columbia, MO; [3]Dept Radiol, Neurol, Psychol Sci., DGS of INP, Univ. of Missouri Columbia, Columbia, MO

Abstract: The core characteristic features of autism spectrum disorder (ASD) include atypical social interaction, impairment in communication, and stereotyped behaviors with restricted activities and interests. Atypical dopaminergic functioning has been shown both in humans with ASD as well as in animal models of ASD. The only FDA approved medications for use in children and adolescents with ASD are the atypical antipsychotic medications risperidone and aripiprazole, inhibiting postsynaptic dopaminergic and serotonergic transmission, which are used to treat irritability. Atypical functional connectivity (FC), the temporal correlation between spatially remote neurophysiological events in the brain, has been observed in ASD. In addition, individuals with ASD sometimes “camouflage” or mask some of their symptoms, especially

during social situations, to be socially accepted. The amygdala is a key brain structure involved in emotion processing, social behavior, and the regulation of emotional responses. Altered FC of the amygdala has been implicated in the social and emotional difficulties that are characteristic of ASD. However, no studies have examined the relationship between dopamine and FC as it relates to camouflaging behavior in ASD. Herein, we examined dopamine transporter (DAT) single photon emission computed tomography (SPECT) and FC of the amygdala and how it relates to camouflaging in fourteen participants (age range = 16-24) with ASD. Participants underwent a dopamine-SPECT scan, resting state fMRI, and completed a questionnaire assessing camouflaging of ASD symptoms which measured the domains of assimilation, compensation, and masking. Half of the participants were found to have abnormal dopamine-SPECT scans, with focal deficits in DAT uptake in the basal ganglia. Furthermore, there were significant differences between the abnormal DAT group and the normal DAT group in assimilation scores, a subdomain of camouflaging. In the abnormal DAT group, FC between the left amygdala and the left lateral cerebellum was significantly negatively correlated with camouflaging, whereas FC between the left amygdala and the cerebellar vermis was significantly negatively correlated with assimilation. This finding highlights the aberrant cerebellum-amygdala pathway that communicates information important for emotion and social circuitry. Our results suggests that dopamine might play role in camouflaging, one of the coping strategies for individuals with ASD, and this relates to amygdalar FC. Further research is necessary to confirm the interplay between dopamine, functional connectivity, and camouflaging in ASD.

Disclosures: N. Nuraini: None. **C. Appling:** None. **B. Ferguson:** None. **D.Q. Beversdorf:** F. Consulting Fees (e.g., advisory boards); Quadrant Biosci, YAMO Pharma, Impel Pharma, Scioto Biosci, and Stalicla Biosci.

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.01/Z32

Topic: I.07. Data Analysis and Statistics

Title: Automated EEG-based depression detection using stacked autoencoder network

Authors: *G. LIN[1], Y. MITSUKURA[2];
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Abstract: Major depressive disorder (MDD) is a medical condition that affects millions of people globally and requires objective and efficient diagnosis. Current subjective diagnosis via clinical interviews and questionnaire is inadequate. Recent advancements in neuroimaging, specifically electroencephalography (EEG), have shown promise in identifying MDD biomarkers. This study introduces a novel automated EEG-based detection system using stacked autoencoders (SAE), which integrates machine learning with EEG data to enhance MDD diagnosis. Methods -We recruited 60 participants, split equally between depression patients and

matched healthy controls. They were all examined per DSM-5 criteria prior to the experiment. Exclusion criteria included comorbid psychiatric disorders and substance abuse. EEG data was bandpass filtered, artifacts removed, and spectral and temporal features extracted. We employed support vector machine (SVM) and SAE for classification, trained on 80% of the data and validated on the remaining 20% with 5-fold cross-validation. Results - Our analysis highlighted significant differences in prefrontal power asymmetry and specific frequency bands between groups. SVM and SAE classifications demonstrated high accuracy, with SVM outperforming SAE in terms of balanced accuracy, F1 score, and Matthews correlation coefficient. Conclusion - This study presents an automated, real-time EEG-based method for MDD diagnosis, offering significant clinical insights and encouraging further research with a larger sample size and additional clinical evaluations.

Disclosures: G. Lin: None. **Y. Mitsukura:** None.

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.02/Z33

Topic: I.07. Data Analysis and Statistics

Support: National Research, Development and Innovation Fund K135837
Hungarian Research Network, SA-114/2021
National Research, Development and Innovation Office, 2021-1.1.4-Fast Gyorsítósáv-2022-00073

Title: Current source density calculation for stereo-EEG data

Authors: *Z. SOMOGYVARI[1,2], K. FURUGLYAS[1], I. BALÁZS[3];
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Abstract: The origin of the EEG signal is the transmembrane Current Source Density (CSD) of the active neuronal populations. Source localization techniques aim to determine the spatial distribution of the CSD to obtain more precise information on the localization of neural activity patterns, based on the measured EEG signals. Stereo EEG (sEEG) data pose specific challenges to CSD calculation methods, as the electrode contact points are arranged irregularly in the 3D volume of the brain tissue. Here, we present a new mathematical method to calculate CSD for any non-regular 3D electrode systems and demonstrate that our method results in more precise source localization than many of the known methods. Traditional CSD calculation methods are based on the assumption that the electrodes form regular 1D, 2D, or in very few cases, 3D grids. In these cases, graph Laplacian calculations using the closest neighboring electrodes provide proper approximations. However, these methods cannot handle irregular electrode arrangements

typical in sEEG measurements. Furthermore, the 1D and 2D approximations neglect the unknown dimensions, which can lead to significant errors in source determination. While model-based inverse methods, like LORETA or kernel CSD, can handle non-regular electrode arrangements, a common drawback is that they cannot handle sources outside the electrode coverage, which is typical in sEEG measurements where the electrode system covers only a small portion of the brain tissue. Significant sources outside the electrode coverage result in huge errors in source determination. In contrast, Laplace-based methods are free from this type of error. Our new Laplace-based calculation method utilizes not only the neighboring electrodes but all available electrodes to achieve the most precise local CSD calculations. The performance of our method was evaluated in simulated experiments with known ground truth CSD distributions. We demonstrated that our method resulted in more precise inference of the CSD than the traditional 1D CSD approximation and compared the performance to the inverse methods as well. The elevated precision of our CSD calculation method can support the localization of the seizure onset zone based on sEEG measurements during surgical planning.

Disclosures: Z. Somogyvari: A. Employment/Salary (full or part-time):; Neunos Ltd., Budapest, Hungary. **K. Furuglyas:** A. Employment/Salary (full or part-time):; Neunos Ltd., Budapest, Hungary. **I. Balázs:** None.

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.03/Z34

Topic: I.07. Data Analysis and Statistics

Support: Vertitas Fund

Title: Detectability of neural responses using spike thresholding and clustering in human intracranial microwire recordings

Authors: *P. N. STEINMETZ[1], J. T. WIXTED[2];
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Abstract: Spike sorting is critical to separating the activity of one neuron in intracranial microwire recordings from the many other neurons nearby in the brain. It is particularly needed in human intracranial microwire recordings given their low signal to noise ratio caused by limitations and noise sources in the clinical environment.
Given the low agreement between the the 4 spike sorting techniques commonly used in this type of recording and consequent lack of consensus on the best technique, we sought to determine the performance of these techniques in detecting changes in the firing rates of putative single neurons. Because ground truth is not available in actual intracranial recordings, we simulated the firing of a single neuron in background activity and noise closely matching the power spectra observed in-vivo. The firing rate of responses and spike amplitudes in these simulations were

chosen to closely match those observed in-vivo and to vary over the range where they begin to cause large changes in detectability.
For 3 of the techniques, Combinato, OSort, and WaveClus, the effect size, measured as total η^2, for event detection only (ignoring clustering), was near the theoretical maximum value of 0.062 when spike amplitudes were greater than 40 µV. For these techniques, clustering decreased performance. For the BML technique, performance for clustering of either single- or multi-unit activity was near the maximum for spike amplitudes between 20-60 uV. Performance based on event detection only was lower.
Thus the optimal technique of the 4 appears to depend on the magnitude of the spike amplitudes being recorded. While these results suggest the clustering step generally does not improve detection of changes in single neuron firing, further exploration of differences between the 4 techniques and their effect on detection is needed.

Disclosures: P.N. Steinmetz: None. **J.T. Wixted:** None.

Poster

PSTR376: Human Data: EEG Recording

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Program #/Poster #: PSTR376.04/Z35

Topic: I.07. Data Analysis and Statistics

Title: Localization and monitoring of workload, fatigue and their combined effects in the brain

Authors: *S. ANGELLIAUME, C. DESHAYES, S. FICARELLA, B. BERBERIAN;
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Abstract: National aviation safety organizations have identified operator fatigue and workload as the main causes of serious incidents. However, the neurophysiological origin and evolution of cognitive fatigue remain largely unknown. The aim of this study is to assess the impact of cognitive load, along with the accumulation of fatigue during time, on executive functions typically necessary to perform piloting-related activities (cognitive control, working memory, cognitive flexibility).Electroencephalogram data have been collected on 16 volunteers that underwent different states of workload and fatigue. For the workload, we use the Multi-Attribute Task Battery II (MATB-II) with two difficulty levels dependent on each subtask-related parameters. Following low vs. high MATB-II task (on separate sessions), participants performed three cognitive tasks aimed at testing the effect of workload level on different cognitive functions. Finally, this paradigm was repeated three times, over the course of each session, in order to test the effect of fatigue. We present herein the results of workload and fatigue on the Simon task, which particularly requires cognitive control functions.Using a Partial Least Square (PLS) analysis in the time domain, we first demonstrate that the two effects manifest themselves in two different brain areas: fatigue mainly in the fronto-central area (p-value < $1e^{-5}$) with a P_{400} amplitude increasing with fatigue and workload mainly in the centro-parietal area (p-value < $1e^{-5}$) with a P_{400} amplitude decreasing with workload. While these 2 effects propagate from

different spatial locations and have opposite impacts on the P_{400} amplitude, we observe significantly (p-value = 0.002) the combined effects in the frontal and fronto-central areas, with a stronger difference (in the P_{400} amplitude) between the two extreme fatigue levels in the lower workload condition than in the higher.Once the combined effects were localized in the brain, we attempted to monitor them. For this, we used a supervised classification method based on machine learning, coupled with a transfer learning technique to overcome the strong issue of inter-individual variability. The method aims at classifying spatial covariance matrices based on a distance defined in the Riemannian geometry. Supervised classification consists in classifying the states of a single subject from a learning base made up of the 15 remaining subjects, and repeating this procedure for each of the available subjects. This inter-individual supervised classification method of combined effects gives an accuracy (mean f1 score) of 72%, which paves the way for monitoring operator fatigue and workload.

Disclosures: S. Angelliaume: None. **C. Deshayes:** None. **S. Ficarella:** None. **B. Berberian:** None.

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.05/Z36

Topic: I.07. Data Analysis and Statistics

Title: Spike sorting in peripheral unmyelinated single nerve fiber recordings in human using ground truth data

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Abstract: Microneurography is an electrophysiological method that captures extracellular action potentials (APs) from peripheral unmyelinated nerve fibers in humans associated with pain signaling. Spike sorting becomes essential as multiple fibers are commonly recorded simultaneously, potentially offering valuable insights into discharge patterns during painful sensations. However, this remains a significant challenge due to low signal-to-noise ratios, the similarity in spike morphologies across fibers, and the employment of a single recording electrode. The current solution involves an indirect spike sorting method based on the marking method. The marking method is an electrical stimulation protocol leveraging that different fibers exhibit distinct conduction velocities when repeatedly stimulated at low frequencies (e.g., 0.25 Hz). This can be visualized by signal segmentation from the repetitive electrical stimulus as action potentials align vertically in time with respect to the stimulus, forming patterns referred to

as tracks. The limiting factor of this method is that it is not a sorting method for APs evoked by additional stimulation, like the injection of pain-inducing chemicals because they diverge from the tracks. It is only observable indirectly through increased latency of the APs evoked by the previous regular pulse because the conduction velocity decreases when the quantity of spikes traveling along the nerve increases. In this work, we created an open-source spike sorting pipeline to assess the potential to use tracked spikes as labeled training data for automating the classification of APs. We analyzed several microneurography recordings and generated ground truth data for responses to regular pulses, along with four recordings tracking responses to both regular and additional electrical stimuli. These stimulation protocols establish class labels for each fiber and enable a systematic and automated analysis of microneurographic recordings. We included seven distinct feature extraction methods and support vector machine (SVM) classification in our pipeline. To evaluate performance and determine the most effective feature sets for each dataset, we utilize standard classification metrics, such as accuracy, precision, recall, and the F1-score. To conclude, our work verifies the possibility of using identified tracked spikes to classify untracked spikes according to their morphology and marks the first step towards automatic spike sorting. It supports assessing the overall sortability of datasets and provides insights into the complexity of the AP morphology recorded via microneurography.

Disclosures: A. Troglio: None. **A. Fiebig:** None. **A. Maxion:** None. **E. Kutafina:** None. **B. Namer:** None.

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.06/Z37

Topic: I.07. Data Analysis and Statistics

Support: JSPS KAKENHI Grant JP23K03875

Title: Detecting predictive signs of epileptic seizures using machine learning

Authors: *H. YOSHIDA[1], R. TANIGUCHI[2];
[1]Kindai Univ., Izumi, OSAKA, Japan; [2]Kindai Univ., Kinokawa, Wakayama, Japan

Abstract: Epilepsy is one of the most common neurological disorders, affecting approximately 50 million people worldwide according to WHO. Epileptic seizures are caused by overexcitation of the whole or part of the brain, making normal cranial nerve activity difficult and causing symptoms such as convulsions and unconscious behavior. Traditionally, epilepsy is diagnosed by specialists identifying interictal epileptiform discharges (IEDs) in EEG data, but visual identification of IEDs from a large amount of EEG data is very difficult. High-Frequency Oscillations (HFO) and Epileptic DC(Slow) shifts (EFD) have also attracted attention in recent years as biomarkers that can be used to detect signs of epileptic seizures. However, issues remain regarding its accuracy as a biomarker and its detection accuracy.Therefore, we introduced a

machine learning-based method to detect predictive signs of epileptic seizures from scalp EEG data. The proposed method is a machine-learning method for detecting abnormal EEG, i.e. signs of epileptic seizures, by constructing a predictor of EEG in the absence of signs of epileptic seizures using only EEG data from the epileptic interictal period. As a discriminator of abnormal EEG, reservoir computing, a special model of recurrent neural network that shows excellent performance in pattern recognition of time series data, was used. The data used were from the CHB-MIT Scalp EEG Database. The results showed that when EEG data immediately before the seizure was input to the proposed discriminator, the prediction error increased, meaning that an abnormal EEG different from the intermittent period was detected. In the future, detailed analysis of the EEG features identified as abnormal EEG is expected to discover new biomarkers of epileptic seizures or to improve the accuracy of conventional biomarker detection.

Disclosures: H. Yoshida: None. **R. Taniguchi:** None.

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.07/Z38

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant UH3NS117944
NIH Grant R01NS112497

Title: An Environment for Synchronous iEEG Acquisition and Real-time Spike Detection Using Dual Brain Interchange Systems

Authors: *A. AYYOUBI[1], C. SWAMY[1], K. J. MILLER[2], G. A. WORRELL[3], N. F. INCE[2]; [1]Neurologic Surgery, Mayo Clin., Rochester, MN; [2]Neurosurg., Mayo Clin., Rochester, MN; [3]Mayo Clin., Rochester, MN

Abstract: The brain-interchange (BIC) system of CorTec is a wireless implantable device that is powered externally, and capable of recording and stimulating from up to 32 channels at a sampling rate of 1kHz. This study introduces a new portable data acquisition setup for simultaneous recording from two BIC systems and a real-time spike detection framework that can be integrated with different amplifiers. The implementation of a dual BIC setup significantly enhances the capacity for invasive neural data recording, allowing access to a broader range of channels (up to 64) and brain sites. This expansion enables the collection of data from regions both inside and outside the epileptogenic zone concurrently. The environment utilizes our established Simulink model, integrating features for system synchronization using a master clock, prolonged recording notification, and status updates via email. The model uses a 10 ms master clock resolution and 64 ms data buffer size by default which results in a maximum of 74ms post-synchronization delay. We demonstrated that the delay can be minimized to as low as 5ms through adjustments in master clock resolution and data buffer size and with higher

computational cost. We further investigated the setup in a real scenario on the prolonged recorded intracranial EEG (iEEG) simultaneously with the clinical system and performed spike detection on the post-synchronized iEEG. Comparison between the dual BIC and clinical systems demonstrated a channel-by-channel agreement in spike rates exceeding 95%. Moreover, the real-time spike detection framework aims to detect interictal spikes in patients with epilepsy as the data is being recorded. Online spike detection was performed over 10-minute long interictal iEEG data recorded with BIC in three human subjects. Detected spikes were then sent via UDP to an external graphical user interface for further processing and visualization. Comparing to a previously published offline detector, the real-time spike detector achieved a 99% similarity index in identifying interictal spikes. Furthermore, our findings indicated that channels with the highest spike rates, captured with BIC, were in the epileptogenic focus. By enabling the online detection of interictal spikes, this study offers early insights into the early prediction of probable seizure onset zone (SOZ), suggesting a promising avenue for enhancing SOZ localization accuracy for clinicians, which is crucial for the surgical treatment of epilepsy.

Disclosures: A. Ayyoubi: None. **C. Swamy:** None. **K.J. Miller:** None. **G.A. Worrell:** None. **N.F. Ince:** None.

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.08/AA1

Topic: I.07. Data Analysis and Statistics

Support: Polish NCN WEAVE-UNISONO grant 2022/04/Y/NZ4/00063.

Title: Animal and human electrical source imaging using kernel methods

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Abstract: Extracellular recordings (LFP, EEG, SEEG) have been a mainstay of neurophysiology for a century. Relatively closely reflecting information processing in the brain they have been used in both animal and human studies, with invasive and noninvasive recordings. The long range of the electric field means that every recording is a mixture of contributions from multiple locations. To identify local contributions to the potential one needs to reconstruct its sources which is usually called current source density analysis in animal studies and electrical source imaging in humans.
Here we overview some kernel approaches to source estimation from multielectrode recordings with arbitrary and possibly hybrid setups (e.g. SEEG and ECoG) - kernel Current Source Density (kCSD), direct kCSD, and kernel Electrical Source Imaging (kESI) - based on different

assumptions and with different level of computational complexity.
We show how each electrode setup combined with specific method of source estimation provides a specific window on the brain activity. We show what we can and what we cannot see with a given method combination. The formal structure of the method allows us to specify precisely the structure of the solution space (eigensources) as well as show what happens to its complement. We show how the problem of aliasing appears naturally in source reconstruction problem and indicate relations with Fourier analysis of randomly sampled signals. We show how one can build insight for the explanatory power of a given setup with simulated data. We illustrate these considerations with results of analysis of multielectrode data recorded in rat's brain and in human preoperative studies of pharmacoresistant patient for estimating location of eloquent tissue.

Disclosures: M. Dovgialo: None. **A. Sawilska:** None. **D.K. Wojcik:** None.

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.09/AA2

Topic: I.07. Data Analysis and Statistics

Support: KKP133871/ KKP20
20391-3/2018/FEKUSTRAT
739593—HCEMM
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Title: Determining the phase of oscillations at epileptic deep sources based on surface EEG measurements

Authors: *K. FURUGLYAS[1,2], M. KIS[1,3,4], B. DR. HORVÁTH[1], A. DR. PEJIN[5,1,4], N. FORGÓ[1,3,4], I. LANGO[1,3], Z. CHADAIDE[1,3,4], T. LASZLOVSZKY[1], Z. SOMOGYVARI[6,1], A. BERENYI[1,3,4,7];
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Abstract: Our objective is to determine the accurate phases of oscillations at deep epileptic sources based on surface EEG measurements. To achieve this goal, we conducted experiments by replaying recorded seizures on deep brain electrodes inserted into human cadavers at various

positions. Simultaneously, EEG signals were recorded on the skull using a 32-channel subcutaneous electrode system, enabling the measurement of phase relations between deep and surface electric potential recordings.
Two distinct methods, the lead-field projection method and the Gabor-Nelson method, were employed to infer deep activity from surface measurements. Both approaches operate under the assumption that the measured signals were generated by a localized deep current source dipole. The lead-field projection method assumes knowledge of the deep source's location, necessitating the solution of the forward model by calculating the lead-fields of unit amplitude dipoles at the known position. This forward solution requires MRI of the head and segmentation of different tissues based on the image.
In contrast, the Gabor-Nelson method does not assume prior knowledge of the deep source's position and only requires information about the electrode positions on the skull, eliminating the need for an MRI image and tissue segmentation.
Comparison of the signals replayed at different intracranial sources to the corresponding reconstructed dipole activity revealed that while the lead-field projection method reconstructed deep sources with slightly greater precision, the Gabor-Nelson method also yielded appropriate results. Our findings provide valuable insights into the comparative efficacy of these methods for accurately determining the phases of deep epileptic sources based on surface EEG measurements.

Disclosures: K. Furuglyas: A. Employment/Salary (full or part-time):; Neunos Ltd. **M. Kis:** A. Employment/Salary (full or part-time):; Neunos Ltd. **B. Dr. Horváth:** A. Employment/Salary (full or part-time):; Neunos Ltd. **A. Dr. Pejin:** A. Employment/Salary (full or part-time):; Neunos Ltd. **N. Forgó:** A. Employment/Salary (full or part-time):; Neunos Ltd. **I. Lango:** A. Employment/Salary (full or part-time):; Neunos Ltd. **Z. Chadaide:** A. Employment/Salary (full or part-time):; Neunos Ltd.. **T. Laszlovszky:** None. **Z. Somogyvari:** A. Employment/Salary (full or part-time):; Neunos Ltd. **A. Berenyi:** A. Employment/Salary (full or part-time):; Neunos Ltd..

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.10/AA3

Topic: I.07. Data Analysis and Statistics

Support: Startup funding from MCW

Title: Dynamic selection of task stimuli based on single neuron responses in humans identified online using Deep Learning

Authors: *S. MATHEW, H. G. REY, A. DOMINGUEZ;
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Abstract: Single-neuron activity can be recorded from patients being evaluated for neurosurgical treatment of drug-resistant epilepsy. These recordings provide an unprecedented window into the human brain to observe how information is encoded and retrieved at the cellular level. Current experimental procedures require laborious offline analysis to identify stimuli eliciting neuronal responses. This delays experimental progress and risks losing valuable neural signals due to the inevitable drift of recording electrodes over time. We introduce a novel system with a software suite for single cell data acquisition and real-time analysis using deep learning, that enables a dynamic experimental framework to identify response-eliciting stimuli, introduce new relevant stimuli, and discard those that fail to elicit responses. This set of tools can dramatically accelerate discovery and open new frontiers in neuroscience research. In a Rapid Serial Visual Presentation (RSVP) experiment, several pictures are presented to the subject multiple times in several blocks. For a block where 180 pictures are shown 6 times each, the recordings from a single probe (8 channels) can generate 1440 (180x8) response rasters, which scales with the number of neurons in each channel. It is common to record from 6-12 probes, which can generate many rasters (>57,600) that needs to be reviewed to identify response-eliciting stimuli. Metrics like response onset and duration, instantaneous firing rate, and statistical tests, can help the review process, but often require manual supervision. RasterNet is an artificial deep neural network that is being developed to categorize each raster as good, bad, or undetermined. RasterNet produces a probabilistic output suggesting how confident the network is that the raster belongs to each class. These probabilities are used to rank the stimuli within each class. The top-ranked responses are then shown to the user at the end of each block for review. Low-ranked stimuli are automatically eliminated, making room for the addition of new stimuli that can be selected based on the top-ranked stimuli. Labeled training data for training the network was created by an expert observer aided by several response metrics associated to each raster. Since most of the rasters were labeled 'bad', good and undetermined classes were oversampled to resolve the class imbalance. The training data was then split to hold 20% of the data as test data. After training, the network predicted the test data with 98% accuracy. The model was then tested on data from other subjects to observe that it could make predictions in line with the response raster ranking created using response metrics.

Disclosures: S. Mathew: None. **H.G. Rey:** None. **A. Dominguez:** None.

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.11/AA4

Topic: I.07. Data Analysis and Statistics

Support: Samuel F. Hulbert Chair Endowment

Title: Machine Learning Strategies to Reduce the Effects of Auditory and Visual Distractors on a Steady-State Visual Evoked Potential Brain-Computer Interface Application

Authors: *A. W. L. CHIU, B. FISHER, D. PAGE, K. TANG, C. RODRIGUEZ REAL, T. CALVIELLO, A. DOUGHERTY;
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Abstract: Steady-state visual evoked potentials (SSVEP) is a non-invasive self-paced brain-computer interface (BCI) paradigm that requires a low demand for cognitive resources. It also possesses a high signal-to-noise ratio (SNR) and information transfer rate (ITR), which makes it a very commonly used technique for BCI device control. However, SSVEPs often require the users to pay attention to the visual stimuli while avoiding visual or auditory environmental distractions. This rigid attention requirement presents a significant barrier when transitioning from controlled laboratory environments to real-world applications. To address this challenge, we developed machine learning strategies capable of mitigating the impact of distractions on SSVEP performance. Our previous work identified potential markers and key EEG features that correlate with the level of cognitive loads and attention that led to poor performance by the BCI users. Specifically, there was a significant negative correlation (maximum $r = -0.5$, $p < 0.01$) between accuracy and mental workload evaluation of the distracting tasks. In this study, we expanded our investigation by evaluating the accuracy of an SSVEP-based BCI in various conditions of mental workload and in the presence of auditory and visual distractions. Our experiment involved 10 participants performing a 4-target SSVEP classification task. Direct application of variations of canonical correlation analysis (CCA) and power spectral density analysis (PSDA) demonstrated that the average classification accuracy across all subjects dropped by over 20% when experiencing any type of visual or auditory distractions. To counteract this decline, we compared several machine learning models (k-NN, FLDA, ANN, and committee of classifiers) using aggregated data from multiple subjects. These generalized models demonstrated the capability to restore SSVEP classification accuracy to levels similar to those observed in the controlled no-distraction condition. This approach has the potential to greatly improve the robustness and practical usability of SSVEP-based BCIs in real-world settings, where distractions are inevitable.

Disclosures: A.W.L. Chiu: None.

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.12/AA5

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant 1R01MH119430

Title: Geometrical and topological motifs of first-episode psychosis in live dyadic interactions

Authors: *R. SINGH[1], D. BHASKAR[1], Y. ZHANG[2], X. ZHANG[3], J. A. NOAH[3], G. WOLF[2], C. TEK[1], V. SRIHARI[1], J. HIRSCH[4], S. KRISHNASWAMY[5];

[1]Yale Univ., New Haven, CT; [2]Mila, Montreal, QC, Canada; [4]Dept. of Psychiatry, [3]Yale Sch. of Med., New Haven, CT; [5]Wu Tsai Institute, Yale Univ., New Haven, CT

Abstract: We present a novel methodology, based on the geometrical and topological characterization of learned representations for classifying first-episode psychosis (FEP) patients vs typically developed (TD) individuals. Our multimodal method utilizes neural recordings from an innovative experimental setup based on the 'two-brain' neuroscience paradigm featuring live face-to-face (dyadic) interactions using simultaneous recordings of functional near infrared spectroscopy, fNIRS, and electroencephalography, EEG. The subject was instructed to gaze at the actor's face on every trial (18 sec) alternated with 12 sec of rest. In condition 1 the actor's gaze was direct and included eye contact, in condition 2 the actor's gaze was indirect without eye-contact. The actor's facial expression was modulated by emotive movie clips not seen by the subject and the subject's facial expressions were recorded as facial action units. Comparison of the direct and indirect gaze conditions, i.e. task-based features (motifs), was used to differentiate between TD and FEP individuals.
Our computational method employs a recurrent encoder-decoder framework to obtain low-dimensional latent trajectories of multimodal, timelapse brain imaging (fNIRS, EEG), and facial action units to record facial expressions, by learning to translate one modality to another. Subsequently, we analyze the shape of the latent trajectories by computing curvature and persistent homology, to assemble a dictionary of 'neural motifs' (patterns of brain activity) associated with face-to-face interactions in TD and FEP subjects. We show that these neural motifs can classify TD and FEP subjects with 79.7% test accuracy (on withheld subjects) and predict the Global Assessment of Functioning (GAF) role scores with the correlation coefficient of 0.48. Our preliminary findings suggest that multimodal representations of fNIRS and theta-band EEG data achieve the best performance. We envisage applications of our methodology in developing diagnostic markers for various neurological disorders in the future.

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Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.13/AA6

Topic: I.07. Data Analysis and Statistics

Title: Purchase Prediction by Prefrontal EEG Analysis Based on Dual Process Theory

Authors: *Y. EDAGAWA[1], S. AOKI[2], Y. KOHATA[3];
[1]Ritsumeikan Univ., Ibaraki, Osaka,, Japan; [2]Dentsu ScienceJam Inc., Tokyo, Japan; [3]DENTSU INC., Tokyo, Japan

Abstract: Predicting consumer purchasing behavior presents significant challenges due to the complex interplay of subconscious and conscious processes that influence decision-making. Traditional approaches, which often rely on self-reported data, may not accurately capture the immediate reactions that guide many purchasing decisions. This research integrates dual-process theory with neuroscientific methods, specifically EEG data analysis, to consider establishing an evaluation method by directly measuring the brain activity involved in purchasing.By employing EEG headsets and eye-tracking technology, in this study, we captured real-time changes in prefrontal brain activity as consumers interact with products, analyzing the interplay between emotional (System 1) and rational (System 2) influences. This method allows researchers to observe the immediate neurological response while consumers see products without the biases inherent in self-reports. The EEG data is segmented into frequency bands that correlate with specific cognitive activities, intuitive reaction (System 1) and rational thinking (System 2), providing patterns of the brain responses during decision-making.We measured emotional changes in the actual in-store purchasing experience, we performed EEG measurements and the subjects walked around among the in-store displayed products. After measuring the EEG in the store, the subjects were given a questionnaire that included recall of the products they remembered, and the products in the subjects' first evoked set were detected. Then, by combining the questionnaire results with those of the EEG analysis, we obtained the following results. When viewing products with high purchase certainty, Fp1 activity increased in the power spectral density (PSD) of the alpha band, and the cross-correlation values between Fp1 and Fp2 were lower than the case viewing products with low purchase certainty, suggesting that it was a positive emotional experience. While our prior research evaluated only the strength of emotion, we found that evaluating the relationship between System 1 and System 2 improved the accuracy of predicting consumers' purchase behavior by 19.1%.

Disclosures: Y. Edagawa: None. **S. Aoki:** None. **Y. Kohata:** None.

Poster

PSTR376: Human Data: EEG Recording

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR376.14/AA7

Topic: I.07. Data Analysis and Statistics

Title: Evaluation of a Novel EEG Device and Algorithm for Recording Neural Data

Authors: *E. FRANTZ[1,2], W. T. PIPER[3], W. AUE[2];
[1]DCS Corp, Beavercreek, OH; [2]Air Force Res. Lab. (AFRL), Wright-Patterson AFB, OH;
[3]Engin., Neurable Inc., Boston, MA

Abstract: Consumer-grade noninvasive neurotechnology to facilitate brain-computer interfacing is a burgeoning market and is a growing contestant to traditional research-grade systems. Research-grade systems (e.g., BioSemi Active2) produce high signal quality and reliable data using wet electrodes but require trained technicians to administer and leaves behind a mess when

removed. Consumer-grade products that involve semi-wet or dry electrodes tend to be faster and more convenient to don outside of the lab but struggle with signal quality issues. The current effort focused on evaluating a consumer-grade, over-the-ear electroencephalography (EEG) device with the potential to bridge the gap between research-grade and consumer-grade systems in assessing attentional states and assessing singal quality of consumer grade technology. The Enten™ from Neurable® embeds a 20-channel dry electrode system in a headphone form factor. Over two days, individuals were evaluated on performance during two cognitive tasks while donning the Enten and a forehead gel-based EEG headset from Neuroelectrics. Individuals completed multiple blocks of both the Multi-Attribute Task Battery - II (MATB-II) and a modified Stroop Task under a distracted and a non-distracted condition. Raw EEG data from the Enten were processed using various pipelines and compared to the Neuroelectrics forehead EEG system. Similarities and differences between the neural data recorded are analyzed and discussed for each device. Implications and considerations for consumer-grade neurotechnology to be leveraged in more naturalistic research settings are discussed

Disclosures: E. Frantz: None. **W.T. Piper:** None. **W. Aue:** None.